Statistical Review and Evaluation

NDA# 19-655/Drug Class 1A by Lawrence R. Hauptman, PhD, "Mathematical Statistician" — R 9 1987

Applicant: Burroughs Wellcome Company

Name of Drug: AZT Capsules

DOCUMENTS REVIEWED: Volumes 2.1,2.20-2.31, December 2, 1986;
Volumes 3.1 and 3.2, January 15, 1987

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1. Background

A. This NDA contains one controlled clinical study entitled, "A Multi-Center Placebo-Controlled Trial to Evaluate Azidothymidine (AZT) in the Treatment of Human Immunodeficiency Virus (HIV) Infections in Patients with Aids Related Complex (ARC) and Acquired Immune Deficiency Syndrome (AIDS)."

B. This study was terminated by the sponsor on the recommendation of an Independent Data Safety Monitoring Board (DSMB) which had been established by the sponsor. The reason for the early termination was the unexpected dramatic difference in mortality between the treatment groups, i.e., 15 placebo deaths vs. 1 AZT death by September 18, 1986. (See Memorandum to Dr. Cooper, IND [illegible] November 26, 1986.) That this difference was unexpected can be seen from the protocol, wherein the evaluation of efficacy was addressed in terms of antiviral effect, restoration of immune response and various specified measures of clinical status. Mortality was not mentioned.

As a result of the early termination of the study, 194 (69%) of the patients did not complete the prescribed duration of treatment.

2. Study Design and Description of the Study Sample

A. The study enrolled patients from 12 centers. The duration of treatment was supposed to be 24 weeks. The dosage was 250 mg every four hours (i.e., six times per day).

B. The protocol specified different inclusion criteria for the AIDS and ARC patients. The intent was to enter advanced ARC patients. Randomization was not, however, stratified by diagnosis (i.e., AIDS or ARC). Randomization was stratified by center, and, within center, by baseline T-helper (T4) cell count. The baseline T4 count was supposed to be the average of three (two pre-entry and one day of entry) determinations. However, inclusion in the defined strata ("Low" if T4 was less than 100 or "High" if T4 was greater than 100) was based on the average of the two pre-entry determinations. Twenty-two patients were placed in the T4 stratum which did not correspond to their baseline T4 count. Although in a small number of cases this was the result of a genuine error, in most cases it was due to reason given above.

C. The primary efficacy variables were death and the occurrence of opportunistic infections (OIs). Secondary efficacy variables included the number of symptoms, the sum of symptom scores, Karnofsky performance status, weight and T4 cell count.

D. The study enrolled 281 patients (144 AZT, 137 placebo). (The NDA usually gives 282 for the number of patients. Patient 1102 (AZT-ARC) was mistakenly disqualified after four days of treatment and was then readmitted as patient 1110 seven weeks later. The sponsor's mortality analyses exclude patient 1102, and are based on 281 patients. All their other analyses include patient 1102. There is some justification for this since events of interest, other than death, could have occurred to that person during the short time that he was patient 1102. However, since mortality is the most important indicator of efficacy in this study, and since there actually were 281 different patients enrolled, I am excluding patient 1102 in my summary of the study sample.) There were 160 AIDS patients (85 AZT, 75 placebo) and 121 ARC patients (59 AZT and 62 placebo). The breakdown by diagnosis and baseline T4 stratum for each treatment is given below.

Table 1

Diagnosis	T4 Stratum	AZT	Placebo
AIDS	LOW	69	63
AIDS	HIGH	16	12
ARC	LOW	22	27
ARC	HIGH	37	35

E. The mean time on study was 120 days for AZT and 116 days for placebo. The corresponding medians were 127 and 120 days.

F. Baseline comparability was assessed by the sponsor with respect to age, weight, Karnofsky score, number of symptoms, sum of symptom scores, T4 cell count and the number of days from the diagnosis of Pneumocystis carinii pneumonia (PCP) until entry. The last of these variables was relevant only for the AIDS patients. The mean number of days since the diagnosis of PCP was significantly longer (p=.04) for placebo (86.6) than for AZT (77.5). None of the other comparisons was statistically significant. In each case the p-value exceeded .15.

3. Statistical Methodology

A. Survival data techniques were used to compare the treatments with respect to the time to death, time to (first) OI, time to Kaposi's sarcoma and time to first transfusion. The sponsor used the Cox Regression analysis or the accelerated failure time model available from SAS. The latter methodology was used when no events occurred in at least one treatment group. When such is the case the Cox Regression analysis cannot be performed. Both of these procedures can be used to adjust the treatment comparisons for other factors (such as diagnosis, T4 stratum, days since diagnosis of PCP, center or log of

baseline T4 cell count) that may affect the occurrence of the event (e.g., death or OI).

I reanalyzed the mortality and OI data using either the Cox Regression analysis from BMDP, which provides more information than does the SAS version, or the accelerated failure time model from SAS. I performed analyses for subsets of the data for which the sponsor did not present analyses. Also, I adjusted for factors, other than treatment, in ways that were more extensive than the sponsor's. For these reasons all of the results reported below that relate to analyses of time to death or time to OI, with one exception, come from my analyses. All other results reported below come from the sponsor's analyses.

B. Stratified Wilcoxon Rank Sum tests (involving the relevant strata defined by diagnosis and T4 stratum, i.e., AIDS-Low, AIDS-High, ARC-Low and ARC-High) were used to analyze baseline comparability, change from baseline for the secondary efficacy variables and change from baseline for the clinical laboratory variables.

C. Mantel's procedure for ordered categorical data (stratified in the same manner as the Wilcoxon Rank Sum tests) was used to analyze the severity of OIs skin test conversions, virology, number of transfusions and adverse reactions.

D. Logistic regression analyses were used to investigate whether certain factors, such as diagnosis, baseline T4 cell count, certain baseline clinical laboratory variables or certain concomitant medications, would increase the risk of hemoglobin or neutrophil toxicities for AZT patients.

E. All reported p-values are two-tailed.

4. Results

A. Mortality Analysis

1) The variable analyzed was the time (in days) from entry to death for patients who died, or the time from entry to study termination for patients who did not die. The latter is called a censored survival time because observation of the event of interest, i.e., death, is cut off or censored as a result of the study termination. Another type of censored survival time occurs when patients drop out of the study and can no longer be observed for the event of interest. Such losses to follow-up did not occur in this study with respect to mortality. At study termination the status (dead or alive) of every patient was ascertained whether or not the patient was still on study.

2) The treatment comparisons given below for various subsets of patients were arrived at after adjusting for other factors which may be related to the risk of death. The log of the T4 cell count is a factor that was adjusted for in all of the analyses. The number of days from diagnosis of PCP was adjusted for in analyses that included only AIDS patients. (This was done because of the significantly larger mean number of days since diagnosis of PCP for the

placebo patients. It was felt that this might indicate that placebo patients had been entered at a later stage in their disease, and that this could have introduced a bias in favor of AZT. However, the analyses did not show this factor to have had a significant effect on the time to death, and its inclusion in the analyses had virtually no effect on the significance of the treatment comparisons.) Diagnosis was adjusted for unless the analysis was restricted to patients from a single diagnosis. Baseline T4 stratum (i.e., High or Low) was adjusted for in the analyses for all patients, AIDS patients and ARC patients.

3) The table below provides the following information for each analysis: the number of deaths (d), the number of patients starting the study (n) and the Kaplan-Meier estimates for the probability of surviving 24 weeks (K-M) for each treatment, the chi-square statistic with one degree of freedom (based on the Score test from the Cox Regression analysis or the Log-Rank test from the accelerated failure time analysis) and the corresponding p-value. The Kaplan-Meier estimate, which is expressed as a percentage for convenience, takes into account the fact that the patients were observed for different lengths of time, and, therefore, had inherently different chances of dying during the study. The crude survival rate, n-d divided by n, which would assume that every patient had the same chance of dying in the study, generally would be different from the Kaplan-Meier estimate. Furthermore, the crude rate has no statistical validity under these circumstances and is not explicitly reported in the table.

Table 2 - Mortality

	AZT			Placebo				
Subset	d	n	K-M	d	n	K-M	χ^2	p-value
All	1	144	98%	19	137	78%	18.13	.0001
Low T4	1	91	96%	15	90	70%	13.04	.0003
High T4	0	53	100%	4	47	91%	5.06	.025
AIDS	1	85	96%	12	75	76%	12.34	.0004
ARC	0	59	100%	7	62	81%	5.83	.016
T4 ≤ 200	1	117	97%	18	109	72%	17.13	.0001
T4 > 200	0	27	100%	1	28	96%	0.93	.34

It is evident from the table that if one considers the results based on all patients, AIDS patients or patients in the low baseline T4 cell count group, then the difference in mortality between AZT and placebo is strikingly impressive. The results based on the ARC patients or the patients in the High baseline T4 cell count group, although statistically significant, are much less impressive.

In order to investigate further the role of the baseline T4 cell count, Dr. Cooper suggested comparing the treatments among patients whose baseline T4 cell count was less than or equal to 200 and among patients for which it was greater than 200. It turned out that when we entered the mortality and OI

data into our computer we used data listings in which the sponsor had rounded-off the log of the T4 cell counts. As a result of this round-off error, I wound up using 220 as the cutpoint instead of the intended 200. Fifty-five patients had baseline T4 cell counts in excess of 220. Five additional patients, none of whom died or had an OI, had counts between 200 and 220. Thus, 60 patients (29 AZT, 31 placebo) had baseline T4 cell counts that were greater than 200. Results based on analyses using 200 as the cutpoint would be very similar to those which used 220, primarily because none of the five patients died. Consequently, analyses using 200 were not performed.

The analysis that included patients with T4 cell counts less than or equal to 220 accounted for all but one of the 20 deaths that occurred. Thus, the treatment comparison among these patients is just as impressive as it was when all patients were considered. In the analysis that included patients with T4 cell counts greater than 220, the treatment comparison was decidedly unimpressive (p=.34). Two items are evident from this analysis. The first is that this subset of patients accounted for only one death (a placebo ARC patient). The second is that not a lot of patients with high T4 cell counts (i.e., > 220) were studied. These patients accounted for approximately 20% of the patient sample.

It turned out that of the 55 patients with T4 cell counts greater than 220, all but six (1 AZT, 5 placebo) were ARC patients. Consequently, any results for patients with T4 counts in excess of 220 are essentially results for ARC patients with T4 counts in excess of 220.

4) Two patients (both placebo ARC patients) died very early in the study, one at 10 days and one at 21 days. It is arguable that these patients were sick enough at entry that they should not have been included in the study. We redid all of the mortality analyses after excluding these two patients. The new analyses showed that after these exclusions the p-value for the treatment comparison among the ARC patients increased from .016 to .045. Also, one of the excluded patients accounted for the only death among patients with T4 counts in excess of 220. Thus, with this patient's exclusion there would be absolutely no evidence (i.e., 0 deaths in 27 patients for each treatment group) of a difference in mortality between AZT and placebo among patients with baseline T4 cell counts greater than 220. The exclusion of these two patients had no impact on any of the other mortality analyses.

Were Placebo patients sicker?

5) At one time in the review process it appeared that one investigator (Investigator #10) might be disqualified. This investigator accounted for two deaths (both placebo ARC patients) among his 19 patients. I reanalyzed the mortality data excluding these 19 patients. The only analyses where these exclusions had any impact were in those for ARC patients, where the p-value increased from .016 to .043 if only Investigator #10's patients were excluded, and increased to .22 if the two early deaths were also excluded. It was finally decided that the disqualification of Investigator #10 was not warranted.

Schooley? yes - he had 19 patients

well, if one "investigator" cheated, perhaps others did.

B. Time to first OI Analysis

1) The variable analyzed was the time (in days) from entry to the first AIDS-defining OI for patients who had an OI, or time to study termination for patients still on study without an OI at study termination, or time to withdrawal for patients who dropped out without an OI prior to study termination. This is different from what was done for the mortality data. Patients who dropped out prior to study termination usually were no longer observed with respect to the occurrence of an OI. Thus, at study termination, although it could be ascertained whether such patients were still alive, it could not be determined whether such patients had had an OI between the time of their withdrawal from the study and the study termination.

2) The same analyses that were performed for the mortality data were also performed for the OI data. The table below provides the same information for OIs as did the previous table for deaths, with two differences. Instead of providing the Kaplan-Meier estimate for the probability of not getting an OI in 24 weeks (which would be analogous to the estimates for the probability of not dying) it seemed to me to be more reasonable to provide the Kaplan-Meier estimate for the probability of getting an OI. Instead of using d to denote the number of deaths, i is used to denote the number of opportunistic infections.

Table 3 - Opportunistic Infections

	AZT			Placebo				
Subset	i	n	K-M	i	n	K-M	χ^2	p-value
All	24	145	23%	46	137	43%	11.93	.0006
Low T4	21	92	39%	34	60	52%	5.76	.017
High T4	3	53	6%	12	77	29%	7.65	.006
AIDS	19	85	36%	32	75	54%	8.15	.004
ARC	5	60	9%	13	62	30%	2.92	.087
T4 < 220	23	118	30%	41	109	51%	9.86	.002
T4 > 220	1	27	4%	4	28	15%	0.58	.45

Although most of the above comparisons were highly statistically significant, these results were generally, except for the group with High T4 cell counts at baseline, less impressive than were the results of the mortality analyses. For two subsets, ARC patients and patients with baseline T4 counts exceeding 220, the treatment comparisons were not significant. In the latter subgroup, as in the mortality analysis, the p-value was considerably larger than .05.

1) The sponsor also presented analyses which excluded OIs that occurred during the first six weeks. The rationale for this was that these early OIs "may have been ongoing but undetected at entry." In actuality patients who had an OI within six weeks were not excluded, rather the occurrence of that OI was ignored. For all such patients their time to OI turned out to be a time censored by study termination or withdrawal. None of the patients had a

second OI. However, if such a patient had had another OI, and it had occurred after six weeks, the time to that OI would have been used in the analysis.

Twenty-four patients (12 AZT, 12 placebo) had OIs which occurred during the first six weeks.

The table below gives the results of my analyses of the time to first OI data after excluding OIs that occurred during the first six weeks. The format is the same as that for Table 3.

Table 4 - Opportunistic Infections Occurring After 6 Weeks

	AZT			Placebo				
Subset	i	n	K-M	i	n	K-M	χ^2	p-value
All	12	145	16%	33	37	36%	17.93	.0001
Low T4	12	92	31%	25	90	44%	8.99	.003
High T4	0	53	0%	8	47	24%	10.25	.002
AIDS	12	85	30%	24	75	45%	8.22	.004
ARC	0	60	0%	9	62	25%	10.56	.002
T4 ≤ 220	12	118	22%	30	109	43%	14.50	.0001
T4 > 220	0	27	0%	3	28	12%	1.17	.28

Since the same number of patients (i.e., twelve) had an OI within six weeks, the exclusion of these OIs ought to magnify the difference between AZT and placebo. This is indeed in what happened for each of the analyzed subsets, as evidenced by the consistently smaller p-values in Table 4 as compared to those in Table 3. Table 4 shows that for the patients treated with AZT, only AIDS patients in the Low T4 stratum had OIs that occurred after six weeks in study.

The treatment comparison for the ARC patients, which was not significant when early OIs were counted (p=.037), was significant when they were excluded (p=.002). The only subset in which the treatment comparison was not significant after the exclusions was in the patients whose baseline T4 count exceeded 220, where the p-value decreased from .45 to .28.

The sponsor didn't explain why six weeks was chosen as the cut-off point. However, examination of the data indicated that the results in Table 4 would be changed little had the cut-off been four or five weeks.

But it's principle! You don't mix in garbage with good data!

4) The exclusion of Investigator #10 would not have had a large impact on the results. The treatment comparisons would have been significant for each of the analyzed subsets, except for patients with baseline T4 counts exceeding 220 (p=.14).

5) In an attempt to investigate whether the AZT dose per unit of weight was related to the occurrence of an OI we requested the sponsor to submit an analysis which assessed the effect of baseline weight on the time to first OI occurring after 6 weeks for AZT-treated AIDS patients. (Note: There were no

such OIs in AZT-treated ARC patients.) Since the starting dose was the same for all patients, baseline weight and baseline dose per unit of weight were inversely proportional. The analysis submitted by the sponsor did not show weight to have had a significant effect on the occurrence of OIs (p=.50).

6) Of the 50 patients (23 AZT, 27 placebo) who received acyclovir therapy for at least two weeks, 12 (3 AZT, 9 placebo) developed an OI. In the remaining 232 patients (122 AZT, 110 placebo), 57 (21 AZT, 36 placebo) developed an OI. Analyses of the time to OI showed a significant difference in favor of AZT among the patients who received acyclovir (p=.025) and among those wo did not (p=.003).

C. Time to Kaposi's Sarcoma Analysis

1) A total of 16 patients (6 AZT, 10 placebo) developed Kaposi's Sarcoma. Ten were AIDS patients (3 AZT, 7 placebo) and six were ARC patients (3 AZT, 3 placebo).

2) None of treatment comparisons was statistically significant (p=.20 for all patients, p=.075 for AIDS patients and p=.99 for ARC patients).

D. Secondary Efficacy Variables

1) The sponsor performed analyses comparing the changes from baseline to 4, 8, 12, 16, 20 and 24 weeks for a number of secondary efficacy variables (number of symptoms, sum of symptom scores, Karnofsky status, weight and T4 cell count). The sponsor presented two sets of analyses. The first set included only those patients who were still in the study and for whom an observation was recorded at the relevant timepoint. (These are called the completers analyses.) The second set makes use of patients who dropped out by carrying forward their last observation. Thus, patients with an observation at 16 weeks, who then dropped out of the study, would be included in the 20- and 24-week analyses using their 16-week observation. (These are called the last observation carried forward (LOCF) analyses.) There was one restriction on this methodology due to the staggered entry of patients and the study's early termination. Observations were not carried forward for a longer period of time than the patient would have been observed for if the patient had not dropped out of the study. For example, a patient with an observation at 12 weeks who, if he had not dropped out, would have completed 18 weeks by study termination would be included in the analyses at 16 weeks but not in the analyses at 20 weeks.

The rationale for the LOCF analyses was that as sicker patients dropped out their poorer scores were no longer taken into account in the completers analyses. Since more placebo patients dropped out the completers analyses would likely be biased against AZT. The LOCF analyses turned out to be slightly more favorable to AZT than did the completers analyses.

2) I will not describe the results of the analyses in detail. In general they exhibited the following pattern:

a) The changes from baseline were statistically significant in favor of AZT at 8 weeks and beyond for Karnofsky status, weight and T4 cell count in the analyses for all patients, for AIDS patients and for patients in the Low baseline T4 cell count group.

b) The above results also held for the number of symptoms and the sum of the symptom scores, except for the 24-week analyses, which were not significant.

c) In the analyses for ARC patients and for patients in the High baseline T4 cell count group none of the comparisons were statistically significant for the number of symptoms, the sum of the symptom scores or Karnofsky status. With respect to weight the results were statistically significant out to 16 weeks for ARC patients, but were generally not significantly different for patients in the High baseline T4 cell count group. With respect to changes in T4 cell count for ARC patients and for patients in the High baseline T4 cell count group the results were statistically significant out to 20 weeks.

d) Nearly all the comparisons between AZT and placebo for the change in T4 cell count were statistically significant in favor of AZT. However, in the later analyses (at 16, 20 and 24 weeks), for certain subsets of patients (AIDS, Low baseline T4 cell count group) the statistically significant difference was more a reflection of a decrease in T4 counts in placebo patients than an increase in T4 counts in AZT patients.

The pattern exhibited by the AZT group as a whole was a large initial increase in T4 cell count followed by a decline over time. The decline was most pronounced in the sicker groups of AZT patients, to the extent that by 16 weeks the median T4 cell count for AIDS patients and the median for Low baseline T4 cell count patients were almost back to their baseline levels. At 16 weeks the median increase for AIDS patients was 3.3 and the median increase for Low baseline T4 cell count patients was 4.3.

E. Clinical Laboratory Variables

1) The sponsor performed analyses comparing the changes from baseline for a variety of clinical laboratory variables. In most cases these analyses were done at 4, 8, 12, 16, 20 and 24 weeks. In two cases, B12 and folate, analyses were at 8, 16 and 24 weeks. The analyses at 24 weeks involved a small segment of the original sample, usually less than 20%. Consequently, I am excluding them from the following summary of these analyses. Unless specified otherwise, the results below refer to the treatment comparisons which considered all of the patients.

a) B12 - significantly larger decrease for AZT (weeks 8 and 16) (difference most evident in AIDS patients and low baseline T4 patients)

b) folate - treatments not significantly different

c) serum creatinine - treatments not significantly different

e) sodium - treatments not significantly different (except week 4, significantly larger decrease for AZT)

f) potassium - treatments not significantly different (~~except week~~ 4, significantly larger decrease for placebo)

g) chlorids - treatments not signifcantly different (except week 4, significantly larger decrease for AZT)

h) bicarbonate - treatments not significantly different

i) bilirubin - significantly larger increase for AZT (weeks 12, 16, and 20)

j) SGOT - significantly larger decrease for AZT (weeks 8, 12 and 20)

k) alkaline phosphatase - significantly larger decrease for AZT (weeks 8 and 12)

l) CPK - significantly larger increase for AZT (weeks 8, 12 and 16)

m) glucose - treatments not signifcantly different

n) amylaze-treatments not significantly different (except week 16, signifcantly larger decrease for AZT)

o) hemoglobin - significantly larger decrease for AZT (weeks 4, 8, 12 and 16) (difference most evident in ARC patients with High baseline T4 counts)

p) hematocrit - significantly larger decrease for AZT (weeks 4, 8, 12 and 16) (difference most evident in ARC patients with High baseline T4 counts)

q) RBC - significantly larger decrease for AZT (weeks 4, 8, 12, 16 and 20) (difference most evident in ARC patients with High baseline T4 counts)

r) reticulocyte count - treatments not significantly different

s) ESR - significantly larger increase for AZT (weeks 4, 8, 12 and 16)

t) platelets - significantly larger increase for AZT (weeks 4, 8, 12 and 16)

u) MCV - significantly larger increase for AZT (weeks 4, 8, 12, 16 and 20)

v) WBC - significantly larger decrease for AZT (weeks 4, 8, 12, 16 and 20)

w) neutrophils - significantly larger decrease for AZT (weeks 4, 8, 12, 16 and 20)

x) lymphocytes - significantly larger increase for AZT (weeks 4, 8, and 12) significantly smaller decrease for AZT (weeks 16 and 20)

y) monocytes - treatments not significantly different (except week 8, significantly larger increase for AZT)

z) eosinophils - treatments not significantly different

aa) basophils - treatments not significantly different

bb) pH - treatments not significantly different

cc) specific gravity - treatment not significantly different (except week 12, significantly larger increase for AZT)

2) It should be noted that the significantly larger decreases in hemoglobin, hematocrit and red blood cell count for the AZT patients were most evident in the ARC patients who were in the High baseline T4 cell count stratum. This was the subset of patients for which there was the least evidence of efficacy.

F) The number of patients who required a transfusion was significantly larger (p=.0001) for AZT than for placebo. The Kaplan-Meier estimates for the probability of requiring a transfusion by Week 24 were .41 for AZT and .16 for placebo. The table below provides the number of patients who were transfused, t, and the sample sizes, n, for various subsets of patients.

Table 5 - Number of transfused patients

Subset	Treatment	t	n
All	AZT	45	145
	placebo	14	137
AIDS	AZT	39	85
	placebo	11	75
ARC	AZT	6	60
	placebo	3	62
Low T4	AZT	37	92
	placebo	13	90
High T4	AZT	8	53
	placebo	1	47

There were significantly more transfusions per patient in the AZT group than in the placebo group for all patients (p=.001), for AIDS patients (p=.001), for patients in the Low baseline T4 group (p=.001) and for patients in the High baseline T4 group (p=.021). The treatment comparison was not significant (p=.24) for patients in the ARC group.

G. The sponsor examined the effect of certain baseline variables (diagnosis, baseline T4 stratum, B12 level, folate level, hemoglobin, white blood count,

neutrophil number and T4 cell count) and certain concomitant medication (acyclovir, ketoconazole, aspirin, acetaminophen and trimethoprin/sulfamethoxazole) on the probability of developing Grade 3 or 4 anemia (hemoglobin <7.5 gm/dl) and on the probability of developing Grade 3 or 4 neutropenia (neutrophils <750) in AZT patients.

The sponsor's methodology forced diagnosis and baseline T4 stratum to remain in the logistic regression model whether or not these factors had a significant effect on the probability of anemia or neutropenia. The other factors entered the model only if they did have a significant effect. It turned out that in each of the analyses the baseline T4 stratum did significantly affect the probabilities of anemia and neutropenia (the probabilities were larger in the Low stratum than in the High stratum) but the diagnosis did not significantly affect those probabilities. None of the other baseline variables and none of the concomitant medications had a significant affect on the probability of anemia. The reason that the actual baseline T4 cell count did not have a significant effect was that most of the effect of the baseline T4 count had already been taken into account through the effect attributed to the difference between the Low and High baseline T4 cell count strata. The estimates of the probabilities of anemia (hemoglobin <7.5 gm/dl) were 35% for AIDS patients and 23% for ARC patients in the Low baseline T4 stratum, and 16% for AIDS patients and 9% for ARC patients in the High baseline T4 stratum.

Three additional baseline variables (B12 level, hemoglobin and neutrophil count) and one concomitant medication (acetaminophen) did have a significant effect on the probability of neutropenia. Lower baseline levels of B12, hemoglobin and neutrophils and longer use of acetaminophen were associated with higher probabilities of neutropenia (neutrophils <750). The estimated probability of neutropenia associated with ten weeks of acetaminophen therapy ranged from 1.6 times as large (AIDS patient in the Low baseline T4 stratum) to 2.5 times as large (ARC patients in the High baseline T4 stratum) as that associated with no acetaminophen therapy.

The sponsor compared the treatment with respect to the severity (i.e., none, mild, moderate or severe) of adverse reactions by body system. These analyses are somewhat more informative than analyses which compare only the proportion of patients who experienced a given adverse reaction. Three adverse reactions were found to have occurred with greater severity (and more often) in the AZT group than in the placebo group. Nausea occurred in 66 of 145 AZT compared to 25 of 137 placebo patients. Myalgia occurred in 11 AZT patients compared to 3 placebo patients. Insomnia occurred in 7 AZT patients compared to 1 placebo patient. (Note: Even though the analyses were based on the severity of the adverse reactions, I have summarized them in terms of the frequency because they are intuitively easier to understand in those terms.)

5. Comments

A. This NDA consists of one controlled clinical trial. Consequently there is no independent confirmatory evidence for the foregoing results or for the

terminated early (13

conclusions that follow from them. Furthermore, the impact of AZT's approval is likely to be that there will not be confirmatory evidence (from placebo-controlled clinical trials) of the efficacy of AZT in the populations for which AZT is indicated. On the other hand, it will be possible, at least in terms of medical ethics, to obtain evidence from placebo-controlled trials to ~~confirm or refute~~ AZT's apparent lack of efficacy for populations of patients for which it is not indicated. Thus it is very important to limit approval to patients for whom evidence of efficacy is particularly strong. It was primarily for this reason that analyses were performed for subsets of patients that had not been prospectively defined in the protocol.

B. We are generally very critical of analyses based on retrospectively determined subgroups. Such analyses usually come about when the overall analysis of all the patients fails to show an investigational drug to be effective (i.e., the overall analysis yields a non-significant result). Analyses on subsets of the patients are then performed in order to determine whether there are any subgroups that will produce a significant treatment comparison. We usually view this as an attempt to salvage a study that, from the sponsor's perspective, produced unsatisfactory results. The validity of such subgroup analyses is weak statistically because, even when a drug is ineffective, random variation can make it appear to be effective in selected subgroups. Furthermore, the more subgroups that are examined, the higher are the chances of finding at least one in which there is a statistically significant treatment comparison.

The subgroup analyses that I performed had a different perspective. In this study the overall analyses (for the major efficacy variables) were highly statistically significant in favor of AZT. The rationale for the subgroup analyses was not to find a subgroup in which AZT was effective, but rather to see if there were subgroups in which there was not strong evidence of efficacy. The reasons for this approach have already been given in the previous section concerning the one controlled trial aspect of the NDA.

Although the protocol did not specify subgroups in which analyses would be performed (indeed it did not address the analysis of the data at all), diagnosis would seem to provide an obvious criterion with which the patients could be grouped (i.e., AIDS or ARC). Since patients were randomized within subgroups that were formed on the basis of whether the patients' baseline T4 cell counts fell below or above 100, analyses within these subgroups (i.e., Low baseline T4 and High baseline T4) are statistically valid. However, Dr. Cooper suggested that subgroups formed on the basis of whether the baseline T4 cell count fell below or above 200 may be clinically more meaningful than those using 100 as the cutoff.

C. This study was terminated early on the basis of interim analyses which showed a large difference in mortality between AZT and placebo. According to the protocol the data were to be examined every eight weeks. When data are examined sequentially in this fashion one cannot perform repeated tests each at the .05 level of significance and still maintain an overall .05 significance level. In order to maintain the overall significance level one

must perform the repeated tests at lower significance levels. Although the protocol did not address this issue, it is my understanding that the DSMB would examine the data four times (August 1, October 1, December 1 and February 1) and would use the O'Brien-Fleming procedure for determining the nominal significance level at each analysis. These turn out to be .00004, .0039, .018 and .041. Thus the mortality data upon which the DSMB recommended terminating the trial, which had been analyzed in preparation for the October 1, 1985 meeting, should have been analyzed using the .0039 nominal significance level. According to my analyses of this data the p-values for the treatment comparisons were .0002 for all patients, .0026 for AIDS patients and .031 for ARC patients. It is arguable that, on the basis of these p-values, the study should not have been terminated for the ARC patients.

Another complication of sequential stopping rules is that all of the various stopping procedures have been developed in the context of testing one variable. Thus, although the procedures specify the significance levels to be used when testing the primary variable (i.e., death, in this study), they do not specify the significance levels to be used to test all of the other variables. What has happened for this study is that once the trial was terminated the sequential stopping aspect of the study was forgotten, and all of subsequent analyses are judged against the usual .05 level of significance.

D. Although many patients violated the protocol (for example, seven patients with T4 cell counts in excess of 500 were entered, ten patients whose time from diagnosis of PCP exceeded 120 days were entered, and 50 patients received prolonged administration of acyclovir while on studies), I have generally adopted an intent-to-treat philosophy and have not excluded any such patients from the analyses. In two cases, however, exclusions were made. Analyses were performed that excluded the two early deaths and analyses were performed that excluded the OIs that occurred prior to six weeks on study. In the one case where the original analyses and the analysis after the exclusions yielded quite different results (i.e., time to OI for ARC patients: p=.027 and p=.002, respectively) I would place greater reliance on the results of the original analysis.

6. Summary

A. The large difference in the number of deaths in the AZT group and the number in the placebo group (i.e., 1 vs. 19) is extremely unlikely (p=.0001) to be due to any factor other than that one group received AZT and the other did not. The estimated 24-week survival rates were 98% in the AZT group and 76% in the placebo group.

The differences were almost as impressive when the analyses were restricted to AIDS patients (1 vs. 12, p=.0004) or to patients in the Low (<100) baseline T4 cell count group (1 vs. 15, p=.0003), but were comparatively less impressive when restricted to the ARC patients (0 vs. 7, p=.016) or to patients in the High (>100) baseline T4 cell count group (0 vs. 4, p=.025).

The above results seemed to indicate that if there were a segment of the study sample that was responsible for most or all of the treatment effect, it was characterized by baseline T4 cell count rather than by diagnosis. This thinking led to the analyses that showed that all but one of the deaths were confined to the group of patients that had baseline T4 cell counts <220. The number of deaths in this group was 1 for AZT and 18 for placebo (p=.0001). The estimated 24-week survival rates were 97% for AZT and 72% for placebo. The number of deaths in the group of patients that had baseline T4 cell counts >220 was 0 for AZT and 1 for placebo (p=.24). The 24-week survival rates were 100% for AZT and 98% for placebo.

It should be noted that only 55 patients (about 20% of the entire sample) had baseline T4 cell counts >220. Due to this small sample size one should not conclude that AZT does not reduce the risk of mortality among patients with baseline T4 cell counts >220, but rather that there is no evidence that it reduces the risk. It should also be noted that over 96% of the AIDS patients had baseline T4 cell counts <220. Thus, conclusions concerning the group with baseline T4 cell counts <220 are essentially conclusions about the AIDS patients or about the ARC patients with a baseline T4 cell count <220, whereas conclusions concerning the group of patients with baseline T4 cell counts >220 are essentially conclusions concerning ARC patients with T4 cell counts >220. (As was stated in the Results section the 220 is an artifact due to round-off error. All of the foregoing would be true if 220 were replaced by 200.)

B. The analyses for the time to first OI were not as impressive as were those for the mortality data. In the overall analyses the number of patients who developed an OI was significantly smaller for AZT than for placebo (24 vs. 45, p=.0006). The estimated 24-week rates for developing an OI were 23% for AZT and 43% for placebo.

The treatment differences were still significant in the analysis restricted to the patients in the Low baseline T4 cell count group (21 vs. 34, p=.017), in the analysis restricted to the patients in the High baseline T4 cell count group (3 vs. 11, p=.006), and in the analysis restricted to the AIDS patients (19 vs. 32, p=.004). The treatment differences were not significant in the analysis restricted to the ARC patients (5 vs. 13, p=.037) unless OIs that occurred during the first six weeks were excluded (0 vs. 9, p=.002).

The analyses that grouped patients on the basis of whether or not their baseline T4 cell counts exceeded 220 gave results that were quite similar to the corresponding analyses of the mortality data. The group of patients that had baseline T4 cell counts <220 accounted for 95% of the deaths and 93% of the OIs. In this group 23 AZT and 41 placebo patients (p=.002) developed OIs. The estimated 24-week rates for developing an OI were 30% for AZT and 51% for placebo. In the group of patients that had baseline T4 cell counts >220, 1 AZT and 4 placebo patients (p=.45) developed OIs. The estimated 24-week rates for developing an OI were 4% for AZT and 15% for placebo. Even if OIs that occurred during the first six weeks were excluded the treatment

comparison among these patients (0 vs. 3) would still not be statistically significant (p=.28).

C. Chronic administration (i.e., at least two weeks) of acyclovir did not appear to affect the occurrence of OIs. About 24% of the patients developed an OI regardless of whether or not they received chronic acyclovir. The treatment comparison was statistically significant in favor of AZT among patients who received acyclovir (p=.025) and among patients who did not (p=.003).

D. The analyses of the changes from baseline for the secondary efficacy variables (number of symptoms, sum of symptom scores, Karnofsky status, weight and T4 cell count) generally mirrored the results of the mortality analyses in the sense that they were more impressive in the AIDS patients and in the patients in the Low baseline T4 cell count group than in the ARC patients or in the patients in the High baseline T4 cell count group. In the former two groups the treatment comparisons were statistically significant out to 20 weeks for all five of the secondary efficacy variables. In the latter two groups the treatment comparisons were statistically significant out to 20 weeks for the T4 cell count, but weren't significant at all for the number of symptoms, the sum of the symptoms scores or the Karnofsky status.

The T4 cell counts in the AZT patients increased sharply during the first four weeks, but declined thereafter. In fact, at 15 weeks the median T4 cell counts for AZT patients in the AIDS group or in the Low baseline T4 cell count group had essentially returned to their baseline levels.

E. The difference in the number of patients that developed Kaposi's Sarcoma (6 AZT, 10 placebo) was not statistically significant (p=.20).

F. Decreases from baseline were significantly larger in the AZT group for hemoglobin, hematocrit and red blood cell count. The differences between treatments were most pronounced in the group of patients for which there was the least evidence of efficacy, i.e., ARC patients who were in the High baseline T4 cell count group.

Decreases from baseline were also signficantly larger in the AZT group for white blood count and neutrophils. For these variables the differences were most evident in the group of patients for which there was the most evidence of efficacy, i.e., AIDS patients who were in the Low baseline T4 cell count group.

G. Significantly more AZT patients required transfusions than did placebo patients (45 vs. 14, p=.0001).

H. In patients treated with AZT the probability of developing anemia (hemoglobin <7.5 gm/dl) and the probability of developing neutropenia (neutrophils <750) were both found to be significantly larger in patients with lower baseline T4 cell counts. The probability of neutropenia was found also to increase significantly in patients with lower baseline levels of B12.

hemoglobin or neutrophils, and in patients with longer durations of acetaminophen therapy.

I. Nausea, myalgia and insomnia occurred to a significantly greater degree in AZT patients than in placebo patients (45.5% vs. 18.2%, 7.6% vs. 2.2% and 4.8% vs. 0.7%, respectively).

7. Conclusions

A. There are a number of disquieting aspects concerning this NDA. It contains only one controlled clinical trial, and thus there is no independent confirmatory evidence for that study's results. It contains a relatively small number of patients (<200) who have been treated with AZT. The controlled clinical study is relatively short (i.e., 24 weeks) and was terminated early on the basis of unanticipated favorable results in a manner that has never been adequately defined in terms of its impact on the subsequent statistical analyses.

B. Despite all of the above, the evidence that AZT is effective is overwhelming. The reduction in the risk of mortality among patients treated with AZT (compared to that among patients treated with placebo) was extremely unlikely to have been the result of chance or any recognizable factor (such as imbalances in the treatment group at baseline with respect to known or suspected prognostic variables, bias in reporting mortality, or imbalances in the treatment group with respect to concomitant medication) other than treatment with AZT itself.

The data also strongly indicate a reduction in the risk of developing an opportunistic infection among patients treated with AZT. These findings are supported by data that generally show beneficial effects with respect to symptomatology, weight, quality of life and immune function.

Almost all of the evidence of AZT's efficacy comes from the group of patients that had baseline T4 cell counts that were less than or equal to 200. This group accounted for nearly all of the AIDS patients in the study. There was only one death, a placebo patient, among the 60 patients that had a baseline T4 cell count in excess of 200.

C. AZT produced hematologic toxicities that were exhibited in a number of ways. AZT patients required more transfusions than did placebo patients. AZT patients had larger decreases in hemoglobin, hematocrit, red blood cell count, white blood cell count and neutrophil counts. Patients with lower baseline T4 cell counts were more likely to develop anemia and neutropenia. Patients with lower baseline hemoglobin and neutrophil counts and longer acetaminophen therapy were more likely to develop neutropenia.

In most cases the toxicities associated with the use of AZT were most evident in the patients that appeared to be deriving the greatest efficacy, i.e., AIDS patients and ARC patients who had low baseline T4 cell counts. However, the decreases in hemoglobin, hematocrit and red blood cell count were most evident

in the group of patients where there was no demonstrable efficacy, i.e., ARC patients with high baseline T4 cell counts.

Laurence M. Hauptman

Laurence M. Hauptman, Ph.D.
Mathematical Statistician

are there other kinds of statisticians?

cc:
HDA 19-085 Orig.
HFM-015
HFM-015/Dr. Cooper
HFM-001/Dr. Bilstad
HFM-084/Dr. Lisook
HFM-710/Dr. Dubey
HFM-713/Dr. Hauptman
Chron
File: DRU 1.3.2
LMHauptman/elh/pcf/3-9-87/0085ln

Concur: Dr. Revius 3/9/87

Dr. Dubey 3-9-87

(19

ÆE STATISTICAL REVIEW OF THE DATA SUBMITTED ON FLOPPY DISC IN THE SUBMISSION OF MARCH 13, 1987 WAS REVIEWED VERBALLY BY THE STATISTICIAN. NO WRITTEN REVIEW WAS PREPARED AND NO MINUTES OR NOTES WERE TAKEN OF THE DISCUSSION.

MISSING Serial FOI (20

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics
Office of Drug Standards

DATE : MAR 2 1987

TO : Edward Tabor, M.D.
Director,
Division of Anti-Infective Products (HFN-815)

FROM : Jerome P. Skelly, Ph.D.
Director,
Division of Biopharmaceutics (HFN-220)

SUBJECT: Biopharmaceutics Recommendation of Approval;

Azidothymidine Capsules NDA 19-655
Burroughs Wellcome Submitted on November 20, 1986

A. Background:

Azidothymidine (AZT) is a potent inhibitor of the in vitro replication of retroviruses including human immunodeficiency virus (HIV). Under the current package insert proposed by the firm, this drug is indicated for the management of certain patients with serious manifestations of infections caused by the HIV. The recommended dosage is 200 to 250 mg (2.5-5.0 mg/kg/dose depending on body weight) q4hr for oral administration. AZT has been recommended for approval by the Advisory Committee held on January 16, 1987.

B. Study Results and Discussion:

1. The pharmacokinetics of AZT has been evaluated in adult patients infected with HIV.

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(3) The bioavailability of 250 mg capsules used in the clinical efficacy studies was evaluated in 5 patients (Formulation No. BJG-01A1, Batch No. 5J2758, dose range 3.8-16.7 mg/kg/q4hr). The bioavailability for this 250 mg capsule was equivalent to that for the IV solution given orally. Drug absorption appears dose independent over the range of 3.8-16.7 mg/kg. The recommended dosage for oral administration is 200-250 mg (2.5-5.0 mg/kg/dose) every 4hrs.

2. AZT is rapidly metabolized to GAZT by glucuronidation. Both compounds are excreted by the kidney. The total urinary recovery was 90% for the oral route.

4. In vitro dissolution data (USP rotating paddle, 50 rpm, using H_2O simulated gastric and intestinal fluid, 37°) supports the comparability of the 100 mg and 250 mg commercial capsule formulations proposed for marketing to the 250 mg capsule formulation used in the clinical and biostudies, and to the 100 mg capsule formulation also used in clinical studies. The dissolution of each tested capsule formulation is pH-independent. A Q◇ dissolved in ○ min was chosen as the specification for dissolution for these commercial capsules.

C. Recommendations:

Given the medical importance of AZT in the treatment of AIDS, the pharmacokinetic/bioavailability studies that were submitted under NDA 19-655 (AZT 100 and 250 mg capsules) are adequate to describe the disposition kinetics of AZT in patients. However, the following additional studies should be considered as possible post-approval requirements (phase IV studies) to more completely define the disposition and performance of AZT capsules.

1. Normally, Division of Biopharmaceutics policy requires that a bioequivalence study in normal subjects be conducted if the product(s) that is tested in the firm's pivotal clinical efficacy and safety studies is formulated differently from the product(s) that is to be marketed. This is to assure that the marketed product(s) will behave the same as the clinically tested product(s). For the NDA 19-655 capsule products that

Wrong missing. (22

were tested in the clinical efficacy studies (100 and 250 mg) and the capsules that was tested in the bioavailability study (250 mg) they are formulated differently from those that are to be marketed. The proposed marketed capsules now contain [redacted] and [redacted]. However, because of concerns for potential toxicity, limited drug supply, the urgency for rapid drug development, the submitted in vivo data and the 250 mg capsule) and in vitro data (dissolution) that strongly suggests that formulation changes for the commercial capsules will have no influence on the AZT bioavailability, the Division of Biopharmaceutics recommends the bioequivalence study can be waived at this time (CFR 320.22 (e)). However, if more clinical trials are considered necessary by the medical officer from HFN-815, we would suggest/recommend that the firm conduct a small scale pharmacokinetic/bioavailability study in patients to characterize the absorption and disposition kinetics of the proposed commercial formulation (250 mg capsules).

2. Both the parent drug AZT and metabolite GAZT are excreted by the kidney. The disposition of these compounds in patients with renal and/or liver failure has not been addressed in the current applications. If there are subpopulations of patients who may have significant renal and/or liver-dysfunction, we would recommend that the firm conduct a limited study (ies) to evaluate the pharmacokinetics of AZT/GAZT in these types of patients to determine if there is a potential for drug/metabolite accumulation which might cause potential side effects/toxicities.

3. Probenecid has been shown to affect the metabolism and elimination kinetics of AZT and this has been noted in the package insert's Drug Interaction Section. Also identified in that same labeling section are other drugs (e.g. aspirin, acetaminophen and indomethacin) that may also affect AZT's disposition. If there are potential clinical safety/efficacy concerns from drug interactions for these drugs or other drugs that are not listed out which are given concomitantly with AZT, limited pharmacokinetic interaction studies may be desirable if the current labeling warning section is felt to be insufficient.

Jerome P. Skelly, Ph.D.

(23

Prepared by Ko-Yu Lo, Ph.D.
RD Initialed by John P. Hunt 2/27/87
FT Initialed by C.T. Viswanathan, Ph.D. CTV 2/27/87

cc: HFN-220 (Skelly, Shulman), HFN-226 (Lo), Chron and Drug files

KYL:smj: 2-27-87

(24

Azidothymidine (AZT, BWA509U)
250 mg capsules

NDA 16-655
Reviewer: Ko-Yu Lo
Wang
3-S
2-D
3-0

Burroughs Wellcome
3030 Cornwallis Rd
Research Triangle Park, NC 27709
Submission Dated:
November 20, 1986 (NDA 19-655)
December 2, 1986 (NDA 19-655)

MAR 2 1987

Review of Pharmacokinetic Studies/Dissolution Studies Protein Binding/Labelling

I. Background

Azidothymidine (AZT) is a potent inhibitor of the in vitro replication of retroviruses including human immunodeficiency virus (HIV). The drug is indicated for the management of certain patients with serious manifestations of infections caused by HIV. Chemically, it is a thymidine analogue in which the 3'-hydroxy (OH) group is replaced by an azido (-N3) group. The agent is a white to beige, odorless, crystalline solid with a molecular weight of 267.24.

In these applications the firm proposes to market AZT 100 mg and 250 mg capsules. The following pharmacokinetic and bioavailability studies are submitted for bio-review:

1. Pharmacokinetic analysis of AZT following oral administration: A report on study P53-01/02, a Phase 1 Study (Doc. No. TBZZ/86/0043)

2. Effect of probenecid on the pharmacokinetics of AZT: An interim report (Doc. No. TBZZ/86/0051)

3. Serum levels of AZT following oral administration of 250 mg capsules in phase II clinical trial patients with AIDS or ARC: Study P53-07 (Doc. No. TBZZ/86/0050)

4. Protein binding of AZT in human, dog and rat plasma (Doc. No. TEIN/85/0003)

5. Dissolution studies (Doc. No. GADR/86/0050, Doc. No. GFZA/86/0339, Doc. No. GAZZ/86/0032)

6. Labelling Capsules)

II. Summary of Studies

The pharmacokinetics and bioavailability of AZT is summarized in the Memorandum dated 1/15/87 and Attachment 1.

III. Individual Study in Detail

1. Study P53-01 (TDZZ/CS/0048)

This study was an open-label, dose-rising, multiple-dose pharmacokinetic study of and oral administration of AZT. The results are documented in Appendix 1.

2. An interim report (TDZZ/CS/0051)

This study examines the effect of probenecid on the pharmacokinetics of AZT. The results are documented in Appendix 2.

3. Study P53-02 (TDZZ/CS/0050)

This study determines the serum levels of AZT after chronic dosing with either 250 mg AZT capsule or corresponding placebo. Samples were collected just prior to a dose and at approximately 1.5 hr after the dose. The results are documented in Appendix 3.

4. Protein binding (TEIK/CS/0003)

The *in vitro* protein binding of AZT in human, dog and rat plasma was documented in Appendix 4.

5. Dissolution studies

(1) The composition of 100 mg, 250 mg capsule formulations and formulation are documented in Appendix 5, Table 1, 2 and 3. The capsule formulations proposed for marketing differ from the capsules used in the clinical trials by only the addition of

(2) Batches of AZT capsules used in the clinical studies and those manufactured according to the intended marketed formulations are listed in Table 4A and 4B. Dissolution profiles (in distilled water) for each of these batches are documented in Table 5A and 5B. The amount of AZT dissolved was determined spectrophotometrically at 265 nm using a semiautomated AutoAnalyzer method. There was no detectable interference from the excipients present in either of the intended marketed capsule strengths 100 mg (batch 6H6016), 250 mg (batch 616011)). The results show that the amount of AZT dissolved after 45 min. is not significantly different for batches used in the clinical studies compared to the intended commercial formulations.

(3) The effect of pH on dissolution of AZT capsules (clinical and commercial formulations) has been examined. The results of the batches tested are summarized in Table 6. Individual data are shown in Table 7-10. None of the batches tested showed significant pH dependence. Comparable results were obtained at 45 min for all formulations in all dissolution media.

(4) Table 11 compares two batches of AZT 100 mg capsules manufactured according to an identical formulation (EKH-01A1). Batch 602742, manufactured using laboratory-scale equipment, dissolved completely in 45 min and passed a six capsule dissolution test of Q= . Batch 6F2704, manufactured using production-scale equipment, failed the six capsule dissolution test, but passed a twelve capsule test. Dissolution rate of AZT capsules was neither significantly affected by the force used to form the capsule plug (Table 12) nor by drug particle size (Table 13), but was affected by lubricant blending time (Table 14). Modification of the formulation to include (in the commercial formulation) as a disintegrant minimized the effect of lubricant over-blending on capsule dissolution rate. The dissolution data for batch 612746 and 612747 (batch size Table 53) were 99.9% and 96.5% in 45 min respectively, which confirms the suitability of the commercial formulation.

VI. Dosage and Administration

The recommended dosage is or 200-250 mg q4hr (2.5-5.0 mg/kg/dose) for oral administration (Attachment 2).

V. Overall Comments

1. The concentration of AZT required to produce a 50% inhibition of HIV replication in vitro (ID_{50}) was less than 0.13 mcg/ml. According to Study P53-01, the mean Cmax and Cmin values for a dosage range of

0.13 mcg/ml

0.16 ~ 0.62 mg/L

Similarly, according to Study P53-02, the mean predose and 1.5 hr postdose AZT levels following chronic administration of 250 mg capsules q4hr for 4 to 12 weeks were 0.16 mcg/ml and 0.62 mcg/ml respectively. Although the serum levels observed following administration of AZT according to the recommended dosage exceeded the ID_{50} of in vitro replication of HIV, the clinical significance of serum concentration of this drug remains to be established since (a) the in vivo antiviral activity of AZT in human is not known and the precise relationships between the in vitro susceptability of virus to AZT and clinical responses to the therapy has not been established and, (b) the toxicity of drug concentration toward various types of cells is currently not available.

2. In this application, the pharmacokinetics of AZT following or oral administration of AZT formulation have been evaluated. The bioavailability of 250 mg capsule formulation has also been determined. However, no bio-study has been conducted for the 100 mg capsule formulation. The 100 mg and 250 mg capsule products that were tested in the clinical studies and the 250 mg capsule product that were tested in the bio-study are formulated differently from those that are to be marketed. In the latter case,
added to minimize the potential lubricant over-blending effect on the dissolution rate of capsules manufactured by a production-scale equipment. Normally, Division of Biopharmaceutics policy requires that a bioequivalence study in normal subjects be conducted if the product that is tested in the firm's pivotal clinical efficacy study is formulated differently from the product that is to be marketed. Due to concerns for potential toxicity, limited drug supply and the urgency for rapid drug development, this type of bioequivalence study has not been carried out. The firm used the following in vivo and in vitro data to support their conclusions that the proposed commercial formulations are bioequivalent to the formulations used in the clinical trials:

The reduced systemic bioavailability of AZT
from the 250 mg clinical trial capsule (64 + 10%) is a result of first-pass metabolism rather than incomplete absorption.

b) The in vitro dissolution data supports the comparability of the 100 mg and 250 mg commercial capsule formulations proposed for marketing to the 250 mg capsule formulation used in clinical trials and the biostudy. These data indicate the lack of influence of pH on the dissolution performance of any capsule formulation. Comparable or improved dissolution was observed for the commercial capsule formulations relative to the clinical trial formulation.

This reviewer tends to concur with the firm in that the formulation changes for the commerical 250 mg capsule will have no influence on AZT bioavailability in man. Since dose size did not influence the bioavailability of the 250 mg clinical capsules, similar results can be anticipated for the 100 mg commercial capsules because the ingredients for these two capsules are almost identical and are relatively dose proportional.

VI. Recommendations:

Given the medical importance of AZT in the treatment of AIDS, the pharmacokinetic/bioavailability studies that were submitted under , 19-655 (AZT 100 and 250 mg capsules) are adequate to describe the disposition kinetics of AZT in patients. However, the following additional studies should be considered as possible post-approval requirements (phase IV studies) to more completely define the disposition and performance of AZT capsules.

1. Normally, Division of Biopharmaceutics policy requires that a bioequivalence study in normal subjects be conducted if the product(s) that is tested in the firm's pivotal clinical efficacy and safety studies is formulated differently from the product(s) that is to be marketed. This is to assure that the marketed product(s) will behave the same as the clinically tested product(s). For the NDA 19-655 capsule products that were tested in the clinical efficacy studies (100 and 250 mg) and the capsule that was tested in the bioavailability study (250 mg) they are formulated differently from those that are to be marketed. The proposed marketed capsules now contain . However, because of concerns for potential toxicity, limited drug supply, the urgency for rapid drug development, the submitted in vivo data (nearly complete absorption for the oral solution and the 250 mg capsule) and in vitro data (dissolution) that strongly suggests that formulation changes for the commercial capsules will have no influence on the AZT bioavailability, the Division of Biopharmaceutics recommends the bioequivalence study can be waived at this time (CFR 320.22 (e)). However, if more clinical trials are considered necessary by the medical officer from HFN-615, we would suggest/recommend that the firm conduct a small scale pharmacokinetic/bioavailability study in patients to characterize the absorption and disposition kinetics of the proposed commercial formulation (250 mg capsules).

2. Both the parent drug AZT and metabolite GAZT are excreted by the kidney. The disposition of these compounds in patients with renal and/or liver failure has not been addressed in the current applications. If there are subpopulations of patients who may have significant renal and/or liver-dysfunction, we would recommend that the firm conduct a limited study(ies) to evaluate the pharmacokinetics of AZT/GAZT in these types of patients to determine if there is a potential for drug/metabolite accumulation which might cause potential side effects/toxicities.

(29

3. Probenecid has been shown to affect the metabolism and elimination kinetics of AZT and this has been noted in the package insert's Drug Interaction Section. Also identified in that same labeling section are other drugs (e.g. aspirin, acetaminophen and indomethacin) that may also affect AZT's disposition. If there are potential clinical safety/efficacy concerns from drug interactions for these drugs or other drugs that are not listed but which are given concomitantly with AZT, limited pharmacokinetic interaction studies may be desirable if the current labeling warning section is felt to be insufficient.

Ko-yu Lo 2/19/87

Ko-yu Lo, Ph.D.
Pharmacokinetics Evaluation Branch

ED Initiated by John P. Hunt 2/18/87
FT Initiated by C.T. Viswanathan, Ph.D. CTV 2/19/87

cc: NDA 19-035 Orig., HFN-140, HFN-225(Lo), HFN-344(Turner), Drug, Chron and FDI files

KTL:lyt:[redacted]2-18-87

(30

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics
Office of Drug Standards

DATE : JUN 15 [illegible]

TO : E. C. Connor, MD
Division of Anti-Infective Drug Products
(HFN-815)

THROUGH: Jerome P. Skelly, Ph.D.
Director,
Division of Biopharmaceutics
(HFN-220)

FROM : Ko-Yu Lo, Ph.D.
Pharmacokinetics Evaluation Branch
Division of Biopharmaceutics
(HFN-226)

SUBJECT: Recommendations for Azidothymidine (AZT)
NDA 19-655

A. Background:

In preparation for the upcoming Advisory Committee Meeting for AZT (1/16/87), a HFN-815 inhouse pre-meeting was held on 1/9/87 to discuss any scientific issues regarding the studies provided in NDA 19-655 (AZT 100 mg and 250 mg capsules). A bio-review of these two applications has been completed at the rough draft stage at the time of this pre-meeting. The medical officer from HFN-815 indicated that she would like to have input from the Division of Biopharmaceutics before the final draft has been processed.
This memo summarizes the bio-review for AZT.

B. Study Results and Discussion:

1. The pharmacokinetics of AZT has been evaluated in adult patients infected with HIV.

(3) The bioavailability of 250 mg capsules used in the clinical efficacy studies was evaluated in 5 patients (dose range 3.8-16.7 mg/kg/dose). The bioavailability for this 250 mg capsule was equivalent to that for the given orally. Drug absorption appears dose independent over the range of 3.8-16.7 mg/kg. The recommended dosage for oral administration is 200-250 mg (2.5-5.0 mg/kg/dose) every 4hrs.

2. AZT is rapidly metabolized to GAZT by glucuronidation. Both compounds are excreted by the kidney. The total urinary recovery was 90% for the oral route.

3. The effect of probenecid on the pharmacokinetics of AZT has been studied in 3 patients with a resulting 3-fold increase of AUC for both AZT and GAZT. The results suggest probenecid may inhibit AZT glucuronidation and decrease the clearance of both AZT and GAZT.

4. In vitro dissolution data (USP rotating paddle, 50 rpm, using H_2O simulated gastric and intestinal fluid, 37°) supports the comparability of the 100 mg and 250 mg commercial capsule formulations proposed for marketing to the 250 mg capsule formulation used in the clinical efficacy studies, and to the 100 mg capsule formulation also used in clinical studies. The dissolution of each tested capsule formulation was pH-independent.

C. Recommendations:

Given the medical importance of AZT in the treatment of AIDS, the pharmacokinetic/bioavailability studies that were submitted under NDA 19-655 (AZT 100 and 250 mg capsules) are adequate to describe the disposition kinetics of AZT in patients. However, the following additional studies should be considered as possible post-approval requirements (phase IV studies) to more completely define the disposition and performance of AZT capsules.

1. Normally, Division of Biopharmaceutics policy requires that a bioequivalence study in normal subjects be conducted if the product(s) that is tested in the firm's pivotal clinical efficacy and safety studies is formulated differently from the product(s) that is to be marketed. This is to assure that the marketed product(s) will behave the same as the clinically tested product(s). For the NDA 19-655 capsule products that were tested in the clinical efficacy studies (100 and 250 mg) and the capsule that was tested in the bioavailability study (250 mg) they are formulated differently from those that are to be marketed. The proposed marketed capsules now contain [redacted]. However, because of concerns for potential toxicity, limited drug supply, the urgency for rapid drug development, the submitted in vivo data (nearly complete absorption for the oral solution and the 250 mg capsule) and in vitro data (dissolution) that strongly suggests that formulation effects for the commercial capsules will have an influence on the AZT bioavailability, the Division of Biopharmaceutics recommends the bioequivalence study can be waived at this time (CFR 320.22 (e)). However, if more clinical trials are considered necessary by the medical officer from HFD-510, we would support/recommend that the firm conduct a small scale pharmacokinetic/bioavailability study in patients to characterize the absorption and disposition kinetics of the proposed commercial formulation (250 mg capsules).

2. Both the parent drug AZT and metabolite GAZT are excreted by the kidney. The disposition of these compounds in patients with renal and/or liver failure has not been addressed in the current applications. If there are subpopulations of patients who may have significant renal and/or liver dysfunction, we would recommend that the firm conduct a limited study (ies) to evaluate the pharmacokinetics of AZT/GAZT in these types of patients to determine if there is a potential for drug/metabolite accumulation which might cause potential side effects/toxicities.

3. Probenecid has been shown to affect the metabolism and elimination kinetics of AZT and this has been noted in the package insert's Drug Interaction Section. Also identified in that same labeling section are other drugs (e.g. aspirin, acetaminophen and indomethacin) that may also affect AZT's disposition. If there are potential clinical safety/efficacy concerns from drug interactions for these drugs or other drugs that are not listed but which are given concomitantly with AZT, limited pharmacokinetic interaction studies may be desirable if the current labeling warning section is felt to be insufficient.

Ko-Yu Lo Ph.D.

Acting Branch Chief John P. Hunt ______

cc: HFD-815 (Dr. E. Tabor), HFD-[illegible] (Skelly, Shulman), HFD-226 (Viswanathan, Hunt, Lo), Chron and Drug files

kyl/lyf [illegible] (1/13/88)

Attachment L

(34)

I. Pharmacokinetic and Bioavailability Studies of BW A509U

Table I

Summary of Pharmacokinetic and Bioavailability Studies for BW A509U

Study	Doc. No.	Subjects	Dosage	Type of Study	Dosage Form	No. Subjects	Principal Findings
PS3-01	TB[illegible]0048	ARC/AIDS patients		Multiple-dose pharmacokinetics		22	
				Evaluation of absolute bioavailability	250 mg capsule, lot 5J2758	18 5	
PS3-01 Amend	TB2206/0051	AIDS patients		Probenecid interaction		3	
PS3-02	TB[illegible]0050	ARC/AIDS patients	250 mg q6hr with some reduction to 250 mg q8hr	Phase II monitoring of plasma BW A509U levels at 1 site	250 mg capsules lots 6A2712 & 6B2740	21	Pre-dose and 1.5 hr levels of 0.12 ± 0.12 and 0.60 ± 0.33 μg/ml

PO = oral, BA = bioavailability

II. Pharmacokinetic Characteristics and Dosage Form Performance of BW A509U in Man

1. Absorption

Following oral administration BW A509U is rapidly absorbed from the gastrointestinal tract with peak concentrations occurring at approximately 0.85 hours after capsule dosing. Urinary recovery of BW A509U plus metabolite averaged 90%, indicating nearly complete absorption of drug substance.

2. Distribution

BW A509U plasma concentrations decline in a biexponential manner indicating two compartmental drug disposition.

BW A509U protein binding in human plasma (determined by ultrafiltration at 37°C) averaged 36% (range [redacted]%) over the concentration range of [redacted] μg/ml

CSF/plasma ratios from 6 patients ranged from 0.15 to 1.35 with an average of 0.5, indicating that BW A509U crosses the blood-brain barrier.

3. Dose Proportionality and Principal Pharmacokinetic Parameters

4. Metabolism

The major route of elimination of BW A509U in man is by glucuronidation to form 5'-glucuronylazidothymidine (GAZT). This metabolite is rapidly formed and cleared from plasma by urinary excretion, with a half-life of about 1 hour. No other metabolites have been identified in human plasma or urine.

5. Excretion

Total recovery ranged from of the doses (mean 77 ± 11%). Following oral dosing (n = 5), urinary recovery of BW A509U ranged from of the dose and GAZT ranged from Total recovery ranged from of the doses (mean 90 ± 15%).

Renal clearance of BW A509U was estimated to be about 400 ml/min/70 kg. This high renal clearance indicates that BW A509U is actively secreted by the renal tubules of the kidney. However, renal elimination represents about

clearance (rapid conversion to GAZT) is responsible for the remaining 60% of BW A509U elimination.

6. Bioavailability

Bioavailability data are available for five patients receiving 250 mg formulated capsules (formulation BJG01A1, batch 5J275G). Patients received one to five capsules (3.8 to 16.7 mg/kg) and the bioavailability ranged from [redacted] with a mean of 64 ± 10%. Dose size did not influence bioavailability. The intersubject variability was quite low. Based on these data, the 250 mg capsule appears to have equivalent bioavailability to BW A509U The 250 mg capsules (identical formulation) were used in the Phase II clinical trial.

7. Effect of Probenecid on the Pharmacokinetics of Azidothymidine (AZT)

Principal pharmacokinetic parameters of BW A509U and GAZT for pre- and post probenecid administration were estimated by noncompartmental methods and are presented in Table 4. After the concurrent administration of probenecid, BW A509U concentrations were higher at all times on day 3 than at the corresponding times on day 1, resulting in approximately a 3-fold increase in the area under the plasma-concentration time curve (AUC). The mean half-life of BW A509U was prolonged during the probenecid treatment (0.92 to 1.52 hr) and there was also a marked decline in BW A509U total body clearance (Cl_{tot}) from 2777 to 1036 ml/min/70 kg. Similar alterations were observed in the disposition of GAZT. Analysis of urinary data revealed a marked reduction in the mean ratio of GAZT/BW A509U from 11.6 to 4.5. These findings suggest that probenecid may inhibit BW A509U glucuronidation and reduce renal excretion of BW A509U and GAZT. The concurrent administration of probenecid may permit a reduction in the frequency of BW A509U dosing in AIDS patients.

III. Dissolution Profiles of BW A509U Capsule Formulations

The 250 mg capsule used in the later stage of the Phase I study and in the Phase II efficacy trial was formulation no. BJG-01A1. Bioavailability data and plasma level monitoring data for this capsule formulation have been discussed above in sections I.1 and I.2, respectively. The 250 mg capsule proposed for marketing (formulation no. BJG-02A1) differs from the clinical trial capsule by only the addition of [redacted] to improve manufacturing and dissolution properties. A 100 mg clinical trial formulation (BKN-01A1) recently has been introduced into clinical trials. The 100 mg capsule proposed for marketing (formulation no. BKN-02A1) is essentially the same formulation as the 250 mg commercial capsule, scaled to 100 mg.

Dissolution profiles in various media were obtained for several batches of BW A509U capsules to compare drug-release rates from the 100 mg and 250 mg capsule commercial formulations to those of the clinical trial formulations (GAZ2/00/0032). The capsules were tested using the USP paddle apparatus at 50 rpm in 900 ml of dissolution media at 37°C. Dissolution was carried out in distilled water, USP simulated gastric fluid without enzyme (SGF, pH 1.2), and USP simulated intestinal fluid without enzyme (SIF, pH 7.5).

A summary of the dissolution results are shown in Table 5. None of the batches tested showed significant dissolution pH dependency. Dissolution results for the 100 mg capsules were marginally higher than the 250 mg capsules in terms of labeled strength dissolved. The commercial formulation had higher dissolution results (reflecting a higher dissolution rate) at the early time intervals, probably due to the presence of the dispersant, sodium starch glycolate, in the formulation.

Table 2

Principal SW A509U Pharmacokinetic Parameters
Following Intravenous Infusion*

Dose-schedule	C_{max} (µg/ml)	C_{min} (µg/ml)	AUC (hr*µg/ml)	Cl_{tot} (ml/min/70kg)	$T_{\frac{1}{2}}$ (hr)
1.0 mg/kg q 8 hr	0.44 ± 0.14	N.D.	0.60 ± 0.17	2141 ± 703	1.09 ± 0.22
2.5 mg/kg q 8 hr	1.17 ± 0.49	N.D.	1.77 ± 0.64	1958 ± 720	1.03 ± 0.23
2.5 mg/kg q 4 hr	1.03 ± 0.03	0.12 ± 0.00	1.63 ± 0.04	1018 ± 48	1.10 ± 0.72
5.0 mg/kg q 4 hr	3.47 ± 0.41	0.16 ± 0.03	3.57 ± 0.51	1705 ± 260	1.13 ± 0.11
7.5 mg/kg q 4 hr	4.71 ± 0.79	0.35 ± 0.16	7.09 ± 0.35	1236 ± 59	0.95 ± 0.24

*Mean ± SD; N.D. = not detectable

Table 3

Principal Bioavailability Parameters
Following Oral Administration of SW A509U Solution*

Dose-schedule	C_{max} (µg/ml)	C_{min} (µg/ml)	T_{max} (hr)	AUC (hr*µg/ml)	$T_{\frac{1}{2}}$ (hr)	F (%)
2.0 mg/kg q 8 hr	0.53 ± 0.11	N.D.	0.42 ± 0.14	0.76 ± 0.17	0.90 ± 0.27	72 ± 1
5.0 mg/kg q 8 hr	1.37 ± 0.53	N.D.	0.48 ± 0.20	2.13 ± 0.40	1.21 ± 0.26	68 ± 25
5.0 mg/kg q 4 hr	1.90 ± 0.93	0.10 ± 0.04	0.50 ± 0.35	2.07 ± 0.33	(-)	63 ± 10
10 mg/kg q 4 hr	2.53 ± 0.74	0.26 ± 0.09	0.70 ± 0.30	4.17 ± 0.54	(-)	60 ± 13

- not determined

Table 4

Pharmacokinetic Parameters of BW A509U
Pre- and Post-Probenecid (PB) Treatment*

Parameter	BW A509U		GAZT	
	Pre-PB	Post-PB	Pre-PB	Post-PB
AUC (µg/ml*hr)	8.08 ± 8.11	2.04 ± 0.58	6.44 ± 1.63	18.0 ± 5.21
C_{max} (ng/ml/70kg)	2777 ± 303	1033 ± 214	(-)	(-)
C_{max} (µg/ml)	0.78 ± 0.19	1.55 ± 0.24	3.62 ± 0.83	4.53 ± 0.45
T_{max} (hr)	0.52 ± 0.22	0.58 ± 0.38	0.75 ± 0.25	1.00 ± 0.25
$T_{\frac{1}{2}}$ (hr)	0.52 ± 0.05	1.52 ± 0.37	1.33 ± 0.40	2.23 ± 0.64

*Mean ± SD. (-) = not determined

Table 5

Dissolution of BW A509U Capsules in Various Media
(Paddle Apparatus, 50 rpm, 900 ml of Dissolution Media)

Labeled Strength	Formulation Use/Batch	Medium	% Labeled Strength BW A509U Dissolved*		
			15 Minutes	30 Minutes	45 Minutes
100 mg	BKN-01A1 CTM/882742	Water	61.4 ± 10.2	88.0 ± 3.5	98.1 ± 1.8
		SGF	73.5 ± 6.3	92.2 ± 6.3	101.7 ± 5.0
		SIF	50.9 ± 5.8	81.0 ± 6.0	93.9 ± 3.8
100 mg	BKN-02A1 COM/882746	Water	89.7 ± 3.3	96.5 ± 3.5	99.9 ± 4.0
		SGF	89.1 ± 1.5	96.7 ± 2.9	100.5 ± 2.4
		SIF	85.7 ± 5.0	95.4 ± 4.3	98.9 ± 2.8
250 mg*	BJG-01A1 CTM/882758	Water	56.8 ± 12.2	82.1 ± 5.1	91.3 ± 4.5
		SGF	57.1 ± 10.4	79.8 ± 6.6	89.1 ± 4.0
		SIF	54.7 ± 7.9	75.8 ± 8.3	85.2 ± 6.7
250 mg	BJG-02A1 COM/881011	Water	81.7 ± 5.0	85.9 ± 6.4	89.6 ± 5.4
		SGF	80.3 ± 4.1	85.2 ± 3.1	86.0 ± 2.6
		SIF	80.3 ± 2.8	86.3 ± 3.6	89.4 ± 4.4

*Mean ± SD
*n = 12, all others were 6 capsules
SGF = simulated gastric fluid without enzyme
SIF = simulated intestinal fluid without enzyme
CTM = clinical trial formulation; COM = commercial formulation

Appendix I study FP53-01 (40 15

I. Title: Pharmacokinetic Analysis of Azidothymidine (AZT) Following Oral Administration: A Report on P53-01, a Phase I Study

Author(s): M. Robert Blum, Sam H.T. Liao, Steven S. Good and Paulo de Miranda

II. MATERIALS AND METHODS

(i) Study Design

The study was originally designed as an open- label, dose-rising, multiple-dose study of intravenous AZT. However, protocol amendment provided for continuation of dosing with orally administered AZT.

. . . . . .

all patients were given oral AZT on a multiple-dose regimen for up to 32 days. Later in the study, a 250 mg formulated capsule (formulation no. BJG01A1, lot 5J2758) replaced Assay and dissolution data for this capsule are presented in Appendix A.

data from five patients were obtained following capsule dosing in the dose range of 250 to 1250 mg (3.8 to 16.7 mg/kg). The multiple-dosing schedule is outlined below:

Dosing Schedule

Patients	Oral*
1 - 4	2.0 mg/kg q 8 hr (3)
5 - 10	5.0 mg/kg q 8 hr (6)
11 - 16	5.0 mg/kg q 4 hr (3)
17 - 23	10.0 mg/kg q 4 hr (5)
24 - 26	15.0 mg/kg q 4 hr (1)

(ii) Assay

Quantitation of AZT levels in plasma was carried out by high performance liquid chromatography (HPLC) at the [redacted] under the direction of Dr. Jerry Collins for the [redacted] patients and at Burroughs Wellcome under the direction of Dr Paulo de Miranda for the [redacted] and [redacted] patients. For the [redacted] patients, analysis of AZT in urine was also performed. Also for the [redacted] patients, plasma and urine were analyzed for 5'-glucuronylazidothymidine (GAZT), a major metabolite of AZT.

The [redacted] method ([redacted]) used a [redacted] column for sample preparation, followed by HPLC separation on a [redacted] column using [redacted] mobile phase of [redacted]. The retention time for AZT was 9 min. The Burroughs Wellcome method ([redacted]) used a gradient system for quantitation of both AZT and GAZT. All samples were heat inactivated at [redacted]C for [redacted] min and ultrafiltered through [redacted]. HPLC separation was carried out on a [redacted] column using a mobile phase of [redacted] linear gradient over 35 minutes. The retention times for GAZT and AZT were 20 and 29 min, respectively. UV detection at 267 nm was used in both methods. The lower limit of detection was approximately [redacted] ng/ml [redacted]. Comparisons of results of samples run by both methods generally agreed within 10% [redacted]

III. RESULTS AND DISCUSSION

~~Patients' demographic and pharmacokinetic data are detailed are presented in Table [redacted]~~ Information on route of drug administration, dosage and schedule for the pharmacokinetic evaluations in each patient is given in Table 2. The number of patients providing data at each schedule is indicated under Materials and Methods. Additional details of individual patient dosing are given in the final medical report of this study (B.W. Doc. No. THRS/85/0002).

The individual plasma levels of AZT™ and GAZT ([redacted] patients only) following intravenous infusion are presented in Tables 3 and 4, respectively, according to the protocol sampling times. Also presented in these tables are mean (± SD) concentrations at the five dose schedules. Because of the short AZT and GAZT half-lives, there was no significant residual concentration from the previous dose. Therefore, plasma levels observed on the single dose phase and those during the multiple-dose phase were pooled to calculate the mean levels. Figure 1 represents plots of the mean AZT plasma concentrations at these schedules. For the every 4 hour schedules, steady-state mean levels were determined over a 4-hour dosing interval and extrapolated, in this

Figure 2 represents plots of the mean AZT™ plasma concentrations following oral dosing in a similar manner to Figure 1.

(i) Pharmacokinetics Following Intravenous Infusion

From semilogarithmic plots of individual data (a typical plot shown in Figure 3), the post-infusion disposition of AZT appears to be biphasic and can be described by a two-compartment model. The pharmacokinetic parameters of AZT and GAZT were estimated by noncompartmental methods and are summarized in Tables 7 and 8. The mean (± SD) AUC values were 0.60 ± 0.17, 1.77 ± 0.03, 1.63 ± 0.04, 3.57 ± 0.51 and 7.09 ± 0.35 hr•μg/ml for the 1 mg/kg q8hr (n = 4), 2.5 mg/kg q8hr (n = 6), 2.5 mg/kg q4hr (n = 2), 5 mg/kg q4hr (n = 7) and 7.5 mg/kg q4hr (n = 3) dose schedules, respectively. The corresponding peak plasma levels (C_{max}) were 0.44 ± 0.14, 1.17 ± 0.49, 1.06 ± 0.03, 2.47 ± 0.41 and 4.71 ± 0.79 μg/ml. There was no significant change in half-life with doses. The overall mean $t_{\frac{1}{2}}$ of AZT was 1.1 hrs. The CL_{tot} was relatively constant (approximately 1900 ml/min/70 kg) from 1 to 5 mg/kg. However, at 7.5 mg/kg (n = 3) it decreased by about 30% (to 1236 ml/min/70 kg) while the $t_{\frac{1}{2}}$ of AZT remained unchanged. It is not clear if this observed change in CL_{tot} is real or an artifact of the small sample size. Additional dose proportionality studies of AZT above 5 mg/kg may be needed if higher doses are to be used in future clinical trials. The estimates of the steady-state volume of distribution (Vd_{ss}) by the noncompartmental method are given in Table 8. The Vd_{ss} was approximately 1.6 L/kg.

CNS involvement of HIV infection has led to a search for drug candidates which can cross the blood-brain barrier. CSF samples were obtained from six of the patients and AZT concentrations in CSF and the CSF/plasma ratios are given in Table 9. The CSF/plasma ratio following

The ratios following oral dosing in two patients were 1.35 and 0.15, respectively. AZT penetration across the blood-brain barrier should be independent of the route of administration. The wide variability in ratios may be dependent on the integrity of the patients meningeal membrane. Overall, the data to date indicate that the CSF/plasma ratio is approximately 0.5. The penetration of AZT™ into CSF is considered a favorable indicator for its continuing clinical development.

Data for the major plasma and urinary metabolite are available for the [redacted] patients. This metabolite has been identified and characterized as 5'-glucuronyl azidothymidine (GAZT). It is the only metabolite recovered in the plasma and urine. The elimination of GAZT appears to be limited by the disposition of the parent drug, as indicated by the proportional decline of GAZT with decline of the parent drug. The mean AUC values of GAZT are [redacted] (n = 1), 4.55 ± 1.59, 4.91 ± 1.46 and 12.83 ± 3.33 hr•μg/ml at the four lower dose schedules, respectively, indicating dose-proportional formation (Table 10).

(ii) Pharmacokinetics and Bioavailability Following Oral Administration of AZT in Solution

Plasma levels for AZT and GAZT are presented in Tables 5 and 6 according to the protocol sampling time.

Mean peak plasma levels (C_{max}) of AZT were

1.5

mg/kg q3hr (n = 6), 5 mg/kg q4hr (n = 3) and 10 mg/kg q4hr (n = 5) dose schedules, respectively. Peak levels generally occurred at 0.5 hr after dosing, indicating rapid absorption. The mean steady-state trough levels (C_{min}) were 0.10 ± 0.04 and 0.26 ± 0.09 μg/ml for the 5 and 10 mg/kg q4 hr dose schedules respectively; no significant accumulation of AZT during the q 8 hr schedule was observed.

The mean bioavailability values, F, were 0.72 ± 0.01, 0.68 ± 0.25, 0.63 ± 0.10 and 0.60 ± 0.13 for the four lower dose schedules. The overall bioavailability was approximately 65%. For most patients who had repeated the oral studies, small intrasubject variabilities in F were observed. Based on the urinary recovery data after oral dosing (Table 13), the incomplete bioavailability is assumed to be the result of first-pass metabolism rather than incomplete absorption. This is indicated by a high total recovery of AZT plus GAZT (89.5 ± 14.8%) following oral dosing and by an increase in the GAZT/AZT ratio following oral administration r

(iii) Urinary Recovery of AZT and GAZT

Urinary recovery data of AZT and GAZT following oral administration of AZT are presented in Table 13 [redacted]

Following oral administration (n = 5), urinary recovery of AZT ranged from [redacted] of the dose and GAZT ranged from [redacted]

(iv) Bioavailability of AZT Oral Capsules

Plasma concentration-time data were obtained from five patients receiving one to five 250 mg AZT capsules (3.8 to 16.7 mg/kg) every 4 hours. The individual plasma levels of AZT and GAZT are presented in [redacted]. The results of bioavailability analysis are summarized in Table 14. The bioavailability (F) of the 250 mg AZT capsule ranged from [redacted] with mean (±SD) of 64 ± 10%. Dose size did not influence bioavailability. The intersubject variability was quite low. Based on these data, the 250 mg capsule appeared to have equivalent bioavailability to AZT solution (Table 11). The 250 mg capsules (identical formulation) were used in the Phase II clinical trial.

IV. CONCLUSIONS

Following oral administration of AZT in solution, the bioavailability was approximately 65% of the dose. Based on urinary data, the decreased bioavailability appears to be due to first-pass metabolism rather than incomplete absorption.

Table 5

AZT™ Plasma Levels (μg/ml) Following Oral Dosing of AZT Solution

Patient ID	Study Day	Time(hr) 0.0	0.25	0.50	0.75	1.0	1.25	1.5	2.0	2.5	3.0	4.0	5.0	*6.0	8.0	8.5
		•••••••••• DOSE = 2.0 MG/KG, Q8HR ••••••••••														
01	DAY 1															
01	DAY 6															
03	DAY 3															
03	DAY 5															
04	DAY 1															
	MEAN	0.00	0.20	0.49	0.34	0.25	.	0.13	0.13	0.07	0.03	0.05	0.03	0.01	0.01	
	±SD	±0.00	±0.23	±0.07	±0.07	±0.03	.	±0.05	±0.06	±0.03	±0.05	±0.04		±0.00	±0.00	
		•••••••••• DOSE = 5.0 MG/KG, Q8HR ••••••••••														
05	DAY 17															
05	DAY 20															
06	DAY 2															
06	DAY 20															
07	DAY 2															
07	DAY 20															
08	DAY 1															
08	DAY 29															
09	DAY 1															
09	DAY 32															
10	DAY 1															
10	DAY 31															
	MEAN	0.03	1.06	1.22	1.16	0.75	0.56	0.55	0.37	0.27	0.18	0.12	0.08	0.05	0.03	
	±SD	±0.09	±0.52	0.63	0.66	0.29	0.12	0.19	0.14	0.12	0.09	0.04	0.01	0.03	0.02	
		•••••••••• DOSE = 5.0 MG/KG, Q4HR ••••••••••														
13	DAY 15															
14	DAY 5															
14	DAY 31															
22	DAY 1															
	MEAN	0.11	1.63	1.21	0.91	0.79	.	0.54	0.37	0.28	0.21	0.09	2.46	.	0.09	1.04
	±SD	0.06	1.14	0.48	0.26	0.15	.	0.12	0.10	0.04	0.01	0.01	1.17	.	0.05	
		•••••••••• DOSE = 10 MG/KG, Q4HR ••••••••••														
17	DAY 6															
18	DAY 1															
18	DAY 25															
19	DAY 4															
21	DAY 4															
23	DAY 1															
23	DAY 19															
	MEAN	0.27	1.43	2.27	2.14	1.75	.	1.16	0.91	0.59	0.48	0.27	2.34		0.16	2.21
	±SD	0.04	1.34	0.73	0.60	0.24	.	0.17	0.40	0.20	0.15	0.08	1.40	.		
		•••••••••• DOSE = 15 MG/KG, Q4HR ••••••••••														
24	DAY 14															

*excluded from the mean calculations because it does not represent a steady-state level (a second dose at 8-hr was not given) or its sample time significantly deviated from the protocol time

Patient ID	Study Day	AUC (hr·µg/ml)	Cmax (µg/ml)	Tmax (hr)	F (%)	$t_{1/2}$ (hr)
01	DAY 1					
01	DAY 8					
	MEAN					
	± SD					
03	DAY 1					
03	DAY 8					
	MEAN					
	± SD					
06	DAY 1					
SCHEDULE	MEAN	0.76	0.53	0.43	72	0.98
	± SD	±0.17	±0.11	±0.14	±1	±0.27

**** 5 mg/kg q 6 hr ****

Patient ID	Study Day	AUC (hr·µg/ml)	Cmax (µg/ml)	Tmax (hr)	F (%)	$t_{1/2}$ (hr)
01	DAY 2					
01	DAY 17					
01	DAY 30					
	MEAN					
	± SD					
05	DAY 30					
07	DAY 2					
07	DAY 30					
	MEAN					
	± SD					
08	DAY 1					
08	DAY 30					
	MEAN					
	± SD					
09	DAY 1					
09	DAY 32					
	MEAN					
	± SD					
10	DAY 1					
10	DAY 31					
	MEAN					
	± SD					
SCHEDULE	MEAN	2.13	1.37	0.38	68	1.2*
	± SD	±0.48	±0.58	±0.20	±25	±0.26

**** 8 mg/kg q 6 hr ****

Patient ID	Study Day	AUC (hr·µg/ml)	Cmax (µg/ml)	Tmax (hr)	F (%)	Cmin (µg/ml)
12	DAY 15					
14	DAY 5					
14	DAY 31					
22	DAY 1					
SCHEDULE	MEAN	2.07	1.90	0.50	63	0.18
	± SD	±0.11	±0.93	±0.35	±19	±0.24

**** 10 mg/kg q 6 hr ****

Patient ID	Study Day	AUC (hr·µg/ml)	Cmax (µg/ml)	Tmax (hr)	F (%)	Cmin (µg/ml)
17	DAY 8					
18	DAY 1					
18	DAY 28					
19	DAY 4					
21	DAY 4					
23	DAY 1					
23	DAY 19					
SCHEDULE	MEAN	4.17	3.53	0.70	60	0.26
	± SD	±0.58	±0.76	±0.30	±18	±0.09

**** 15 mg/kg q 6 hr ****

Patient	Study	AUC	Cmax	Tmax	F	Cmin

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Patient ID	Study Day	AUC	Cmax	Tmax	F	$t_{1/2}$
01	DAY 1					
01	DAY 5					
	MEAN					
	±SD					
02	DAY 1					
02	DAY 5					
	MEAN					
	±SD					
06	DAY 1					
SCHEDULE	MEAN	0.76	0.53	0.42	72	0.98
	±SD	±0.17	±0.11	±0.14	±1	±0.27

**** 5 mg/kg q 8hr ****

Patient ID	Study Day	AUC	Cmax	Tmax	F	$t_{1/2}$
05	DAY 2					
05	DAY 17					
05	DAY 30					
	MEAN					
	±SD					
06	DAY 30					
07	DAY 2					
07	DAY 30					
	MEAN					
	±SD					
08	DAY 1					
08	DAY 30					
	MEAN					
	±SD					
09	DAY 1					
09	DAY 32					
	MEAN					
	±SD					
10	DAY 1					
10	DAY 31					
	MEAN					
	±SD					
SCHEDULE	MEAN	1.13	1.37	0.48	60	1.2*
	±SD	±0.40	±0.58	±0.30	±25	±0.26

*** 5.0 mg/kg q 8 hr ***

Patient ID	Study Day	AUC (hr·µg/ml)	Cmax (µg/ml)	Tmax (hr)	F (%)	Cmin (µg/ml)
13	DAY 15					
14	DAY 5					
14	DAY 31					
22	DAY 1					
SCHEDULE	MEAN	2.07	1.90	0.50	63	0.10
	±SD	±0.33	±0.93	±0.35	±19	±0.04

**** 10 mg/kg q 8 hr ****

Patient ID	Study Day	AUC (hr·µg/ml)	Cmax (µg/ml)	Tmax (hr)	F (%)	Cmin (µg/ml)
17	DAY 8					
18	DAY 1					
18	DAY 28					
19	DAY 4					
21	DAY 4					
23	DAY 1					
23	DAY 19					
SCHEDULE	MEAN	4.17	3.53	0.70	60	0.26
	±SD	±0.56	±0.76	±0.30	±18	±0.09

**** 15 mg/kg q 8 hr ****

Patient	Study	AUC	Cmax	Tmax	F	Cmin

Table 5

GAZT Plasma Levels (µg/ml) Following Oral Dosing of AZT*

Patient ID	Study Day	Time (hr) 0.0	0.25	0.50	0.75	1.0	1.25	1.5	2.0	2.5	3.0	4.0	5.0	6.0	8.0	8.5
		********** DOSE = 2.0 MG/KG, Q8HR **********														
03	DAY 3															
03	DAY 5															
	MEAN															
	±SD															
		********** DOSE = 5.0 MG/KG, Q8HR **********														
06	DAY 30															
07	DAY 2															
07	DAY 30															
09	DAY 1															
09	DAY 32															
	MEAN	0.02	1.66	3.93	6.64	6.54		4.63	3.29	2.53	1.77	0.99	0.44	0.27	0.10	
	±SD	±0.04	±0.96	±2.18	±4.47	±3.52		±1.34	±0.74	±0.80	±0.60	±0.37	±0.08	±0.07	±0.06	
		********** DOSE = 5.0 MG/KG, Q4HR **********														
13	DAY 15															
14	DAY 5															
14	DAY 31															
	MEAN	0.04	3.62	5.40	6.43	6.08		4.85	3.28	2.28	1.67	1.17	8.31		0.64	3.14
	±SD	0.59	3.51	2.86	2.51	2.91		1.90	0.91	0.62	0.48		2.98		0.48	
		********** DOSE = 10 MG/KG, Q4HR **********														
17	DAY 6															
19	DAY 4															
21	DAY 4															
23	DAY 1															
23	DAY 19															
	MEAN	2.55	4.18	10.01	15.55	14.66		11.41	8.53	5.15	3.83	1.98	9.31	7.07	2.11	22.76
	±SD	0.32	2.22	4.75	4.61	5.91		2.97	2.88	1.57	1.31	0.64	4.27		0.42	

*excluded from the mean calculations because it does not represent a steady-state level (a second dose at 4-hr was not given)

Table 12

Pharmacokinetics of GA2T Following Oral Administration of AZT™

**** 2.0 mg/kg q 8 hr ****

Patient ID	Study Day	AUC (hr•ug/ml)	Cmax (ug/ml)	Tmax (hr)	t½ (hr)
03	DAY 3				
03	DAY 5				
SCHEDULE MEAN ±SD					

**** 5.0 mg/kg q 8 hr ****

Patient ID	Study Day	AUC (hr•ug/ml)	Cmax (ug/ml)	Tmax (hr)	t½ (hr)
06	DAY 30				
07	DAY 2				
07	DAY 30				
	MEAN ±SD				
09	DAY 1				
09	DAY 32				
	MEAN ±SD				
SCHEDULE MEAN ±SD		12.83 ±4.21	6.01 ±3.57	1.08 ±0.14	1.10 ±0.14

**** 5.0 mg/kg q 4 hr ****

Patient ID	Study Day	AUC (hr•ug/ml)	Cmax (ug/ml)	Tmax (hr)	Cmin (ug/ml)
13	DAY 15				
14	DAY 5				
14	DAY 31				
SCHEDULE MEAN ±SD		12.74 ±7.67	7.18 ±2.44	0.75 ±0.25	0.69 ±0.42

**** 10 mg/kg q 4 hr ****

Patient ID	Study Day	AUC (hr•ug/ml)	Cmax (ug/ml)	Tmax (hr)	Cmin (ug/ml)
17	DAY 6				
19	DAY 4				
21	DAY 4				
23	DAY 1				
23	DAY 19				
SCHEDULE MEAN ±SD		28.91 ±7.56	15.76 ±5.20	1.11 ±0.29	1.98 ±0.64

Table 13
Urinary Recoveries of AZT™ and GAZT Following Oral Administration of AZT

			Oral Administration				
3 - TMC	1	2 mg/kg, po, q3h	0-3 hr				4.6
6 - GRP	1	5 mg/kg, po, q3h	0-3 hr				3.6
13 - BLS	12	5 mg/kg, po, q4h	0-12 hr				2.7
	31	5 mg/kg, po	0-4 hr				9.4
			Mean				6.0
			± SD				± 4.8
14 - PTH	3	5 mg/kg, po, q4h	0-8 hr				8.4
	31	5 mg/kg, po	0-4 hr				6.2
			Mean				7.3
			± SD				± 1.6
17 - CZS	32	10 mg/kg, po	0-4 hr				6.8
			Overall Mean	14.3	75.2	89.5	5.7
			± SD	± 2.8	± 14.6	± 14.8	± 1.6

*excluded from the Mean calculation

(50

Table 14

Summary of Bioavailability of AZT™ Oral Capsules

Patient ID	Dose (mg)	Dose (mg/kg)	AUC (hr•µg/ml)	Cmax (µg/ml)	Tmax (hr)	CL/F (ml/min)	F (%)	Oral Sol. F (%)
13	250	3.8						
17	750	9.2						
19	750	10.2						
24	1000	13.3						
26	1250	16.7						
		MEAN	1.80	1.18	0.85	2572	64	
		±SD	±0.65	±0.59	±0.42	±890	±10	
		cv %	36	50	49	35	16	

*Mean and standard deviation calculations of AUC and C_{max} were dose-normalized to one 250 mg capsule.

Table 14A AZT Plasma Levels (µg/ml) Following Oral Dosing of 250 mg AZT Capsules

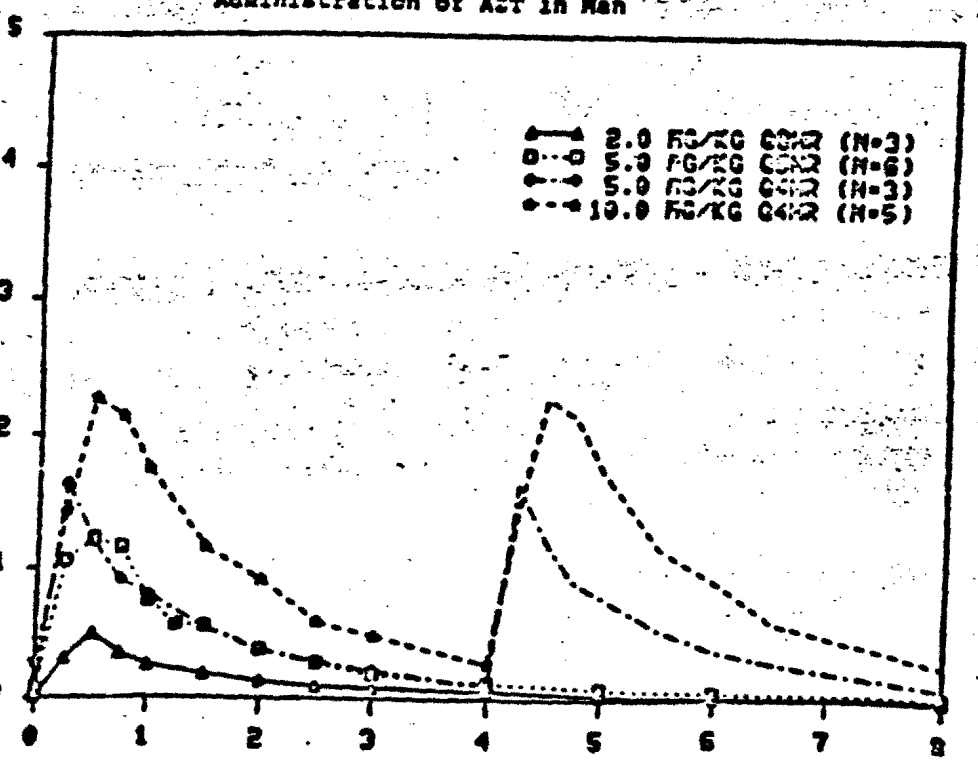
Patient ID	No. of Capsules	Time (hr) 0.0	0.25	0.50	0.75	1.0	1.25	1.5	2.0	2.5	3.0	4.0	5.0	6.0	8.0
13	1														
17	3														
19	3														
24	4														
26	5														
	MEAN*	0.07	0.18	0.83	0.64	1.02	1.17	0.73	0.38	0.27	0.19	0.10	0.03	-	-
	± SD	±0.09	±0.24	±0.87	±0.84	±0.49	±0.29	±0.11	±0.05	±0.08	±0.07	±0.04	±0.03		

GAZT Plasma Levels (µg/ml) Following Oral Dosing of 250 mg AZT Capsules

Patient ID	No. of Capsules	Time (hr) 0.0	0.25	0.50	0.75	1.0	1.25	1.5	2.0	2.5	3.0	4.0	5.0	6.0	8.0
13	1														
17	3														
19	3														
	MEAN*	0.39	0.70	1.75	2.40	3.47	-	6.00	4.99	3.23	2.02	0.99	0.51	0.28	0.15
	± SD	±0.27	±0.07	±2.62	±3.54	±3.08	-	±1.20	±0.66	±0.64	±0.41	±0.11	±0.11	±0.02	±0.05

*Mean and standard deviation calculations were dose-normalized to one 250 mg AZT capsule.

Figure 2: Mean Plasma Concentration-Time Profile of AZT Following Oral Administration of AZT in Man



Appendix 2 - Interim Report (TB 22/86/0054) (53)

Title: Effect of Probenecid on the Pharmacokinetics of Azidothymidine (AZT): An Interim Report

Author(s): Paulo de Miranda, Steven S. Good, Sam H.T. Liao and M. Robert Blum

MATERIAL AND METHODS

Study Design

As a protocol amendment to the Phase I study of AZT (3), five patients with acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC) receiving AZT therapy at the National Cancer Institute were selected for this study. To date data are available for three of these patients and represent the basis for this interim report.

On day 1 patients were given oral solutions of AZT at a dose of 2 mg/kg at 8:00 a.m., 4:00 p.m. and 12:00 a.m. Blood samples were collected 0.0, 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0 and 8.0 hrs following the 8:00 a.m. dose for pharmacokinetic analysis. On day 2 the patients continued with the AZT regimen and were also given 500 mg of probenecid orally at 6:00 a.m., 12:00 p.m., 6:00 p.m., and 12:00 a.m. On day 3 they continued taking 500 mg probenecid at 6:00 a.m., 12:00 p.m. and 6:00 p.m. and were given a single dose of 2 mg/kg AZT at 8:00 a.m. Blood samples were obtained as on day 1. Each blood sample was centrifuged to obtain the plasma. The samples were stored in appropriate tubes at [redacted]C. Total urine collections were made daily

Assay

AZT and GAZT concentrations in plasma and urine were determined by reversed-phase high-performance liquid chromatography (HPLC). Prior to analysis each plasma or urine sample was heat-inactivated at [redacted]C for [redacted] minutes and clarified by ultrafiltration using a Centrifree Micropartition System [redacted] Briefly, the HPLC analysis was performed on a [redacted] reversed-phase column using a mobile phase of [redacted] minutes. The retention times for GAZT and AZT were [redacted] and [redacted] minutes, respectively, and

their 267 nm UV peak areas were linearly related to the concentrations of AZT aqueous standards. The lower limit of detection was approximately [redacted] ng/ml. Complete details of the assay appear in the pharamacokinetic report of the Phase I study [redacted].

RESULTS AND CONCLUSIONS

The three patients of this interim report; [redacted] corresponded to patients 10, 1, and 5 of the Phase I study [redacted]. ~~Demographic information for these individuals is presented in Table 1 and~~ individual plasma levels are given in Table 2. Figure 1 shows mean AZT and GAZT levels pre- and post-probenecid. The pharmacokinetic parameters of pre- and post-probenecid treatment are presented in Table 3 for AZT and Table 4 for GAZT. Urinary excretion data for both drug and metabolite are given in Table 5.

The following results were observed:

1. Coadministration of probenecid with AZT resulted in a marked elevation in the plasma levels of AZT resulting in approximately a three-fold increase in AUC and a corresponding decline in total body clearance. The mean half-life of AZT increased from 0.92 to 1.52 hr during coadministration of probenecid

2. Probenecid treatment also resulted in a nearly three-fold elevation of AUC for GAZT and an increase in its mean half-life from 1.33 to 2.23 hrs.

3. The mean GAZT/AZT urinary excretion ratio declined from 11.6 ± 6.3 to 3.5 ± 1.3 after probenecid coadministration.

These data suggest that probenecid may inhibit AZT glucuronidation as well as decrease AZT and GAZT tubular secretion resulting in a marked decline in the clearance of both drug and metabolite. The concurrent administration of probenecid with AZT may help reduce the frequency of AZT dosing in AIDS patients.

Reviewer's Comment: I concur with the firm in their conclusions

Table 2
Plasma Concentrations of AZT and GAZT Following Oral Administration of AZT Pre- and Post- Probenecid Treatment

AZT Plasma Level (µg/ml)

Patient ID		0.0	0.25	0.50	0.75	1.0	1.25	1.5	2.0	2.5	3.0	4.0	5.0	8.0
****** pre-probenecid **********														
01														
05														
10														
Mean		0.02	0.09	0.72	0.55	0.36	0.25	0.23	0.13	0.10	0.06	0.03		
±SD		0.02	0.08	0.28	0.13	0.07	0.06	0.01	0.01	0.01	0.00	0.00		
****** post-probenecid **********														
01														
05														
10														
Mean		0.05	1.16	1.09	1.09	0.93	0.74	0.61	0.42	0.30	0.23	0.14	0.05	0.04
±SD		0.10	0.03	0.43	0.03	0.14	0.10	0.11	0.07	0.03	0.05	0.03	0.03	

GAZT Plasma Level (µg/ml)

Patient ID		0.0	0.25	0.50	0.75	1.0	1.25	1.5	2.0	2.5	3.0	4.0	5.0	8.0
****** pre-probenecid **********														
01														
05														
10														
Mean		0.17	0.03	2.70	3.03	3.17	2.53	2.05	1.31	0.04	0.00	0.33	0.14	0.03
±SD		0.16	0.04	1.35	0.77	0.53	0.20	0.49	0.37	0.33	0.19	0.11	0.05	0.02
******* post-probenecid *********														
01														
05														
10														
Mean		0.55	1.22	3.04	3.59	4.01	5.03	4.62	4.07	3.36	2.76	2.03	1.04	0.55
±SD		0.66	1.03	1.91	1.77	0.60	0.64	0.81	0.69	0.54	0.62	0.55	0.45	0.38

(54

Table 3

Pharmacokinetic Parameters of AZT Pre- and Post-Probenecid (PB) Treatment

Treatment	Patient	AUC (μg/ml·hr)	C_{max} (μg/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	CL_{tot}/F (ml/min/70 kg)
AZT						
Mean		0 86	0 79	0 52	0 92	2777
± SD		0 11	0 19	0 22	0 06	323
AZT/PB						
Mean		2 44	1 55	0 58	1 52	1026
± SD		0 53	0 24	0 28	0 37	214

Table 4

Pharmacokinetic Parameters of GAZT Pre- and Post-Probenecid Treatment

Treatment	Patient	AUC (μg/ml·hr)	C_{max} (μg/ml)	T_{max} (hrs)	$t_{1/2}$ (hr)
AZT					
Mean		6 44	3 62	0 75	1 33
± SD		1 83	0 63	0 25	0 43
AZT/PB					
Mean		18 02	4 58	1 00	2 23
± SD		5 21	0 45	0 25	0 64

Table 5

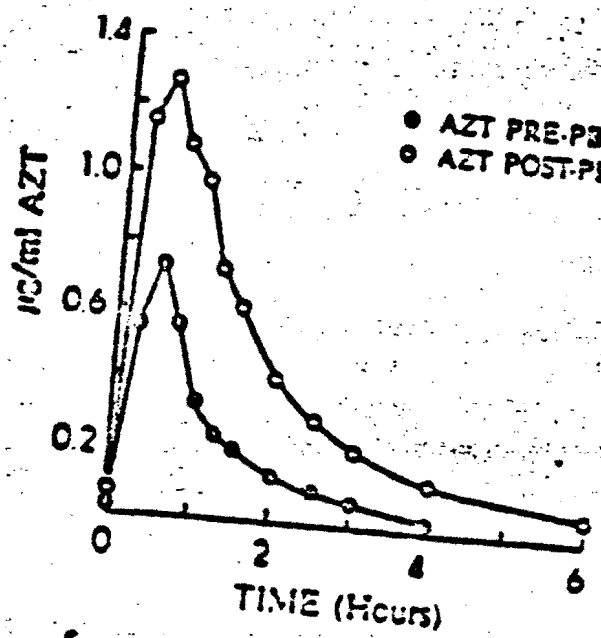
Urinary Excretion (24 hr) of AZT and GAZT Pre- and Post-Probenecid Treatment

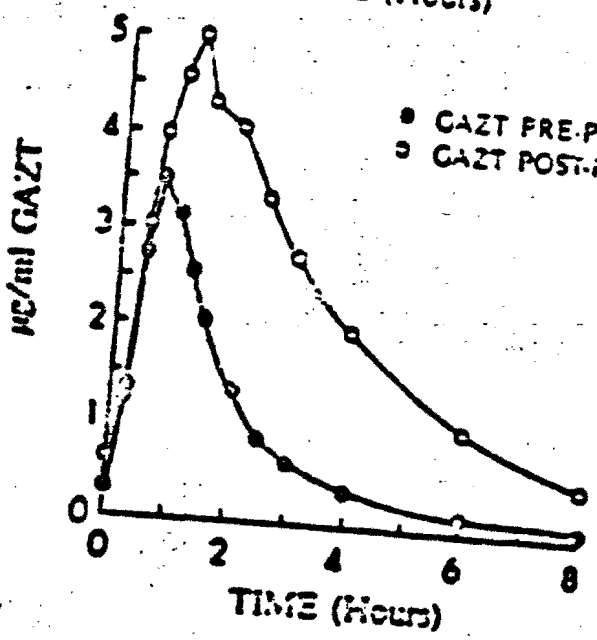
Patient ID	Treatment Mode	Urinary Excretion (mg) AZT	Urinary Excretion (mg) GAZT	GAZT/AZT
	PRE-PB			
	POST-PB			
	PRE-PB			
	POST-PB			
	PRE-PB			
	POST-PB			
	PRE-PB (Mean ± SD)			11 6 ± 6.3
	POST-PB (Mean ± SD)			4 5 ± 1 3

(57 =7

FIGURE 1

PLASMA CONCENTRATION-TIME PROFILES OF AZT AND GAZT. MEAN PLASMA LEVELS PRE- AND POST-PROBENECID





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Medical officer Review

(59

Medical Officer Review of NDA 19-856

Date Submitted: December 2, 1986
Date Received: December 3, 1986
MOR Completed: March 9, 1987

Sponsor: Burroughs Wellcome Company
3030 Cornwallis Road
Research Triangle Park, North Carolina

Drug: Chemical: 3'-azido-3'-deoxythymidine
Generic: zidovudine
Trade: Retrovir

Classification: Antiviral (AIDS) Category: 1AA

Dosage Form and Route of Administration: 100 mg capsules for oral administration

Proposed Indication: The management of certain patients with serious manifestations of infections caused by the human immunodeficiency virus (HIV).

Related NDA's:

Related IND's:

Manufacturing and Controls: Please see Chemistry Review by John Taylor, Ph.D., dated January 7, 1987. Azidothymidine is synthesized from
Although production has increased tremendously over the past few months, there is still a limited supply.

Pharmacokinetics: Please see Biopharmacology Review by Ko-Yu Lo, Ph.D., dated March 2, 1987. Briefly, AZT capsules are well absorbed after oral administration (bioavailability is 65% compared to the formulation). Peak concentrations occur approximately one half hour following oral administration, and the half life is approximately one hour. AZT is rapidly catabolized by glucuronidation to GAZT, which has no demonstrable antiviral activity. Urinary recovery after oral administration consists almost entirely of this metabolite and unchanged drug.

Pharmacology/Toxicology: Please see Pharmacology/Toxicology reviews by Harvey Clemow, Ph.D., dated December 29, 1986, February 13, 1987, and March 6, 1987. Briefly, three month subchronic toxicity studies of AZT administered by the oral route have been completed for two species, the rat and cynomolgus monkey. Six month studies have also been performed in these two species; the final report of the rat study was submitted on February 10, 1987, and showed no treatment-related findings except for a mild anemia. One year toxicity studies in the same two species were initiated in February and March 1987. A carcinogenicity study in rats was begun in January and one in mice is scheduled to begin in April 1987.

Microbiology: Please see Microbiology Review (Drug Control Notes) by James C. [redacted], PhD. dated February 9, 1987. Briefly, AZT is active in vitro against HIV at concentrations ranging from < 0.13 ug/ml (IC50 when AZT was added shortly after laboratory infection of susceptible cells) to > 13 ug/ml (Prophylactic inhibition of HIV activity in chronically infected cell lines). AZT also has activity against several other mammalian retroviruses, but has no significant activity against a variety of other human and animal viruses. It inhibits certain gram negative bacteria (Enterobacteriaceae) at low concentrations (0.063 to 0.5 ug/ml) and Giardia lamblia at 1.0ug/ml, but has no demonstrable activity against other protozoal pathogens or against many common fungi.

Clinical Background: After demonstration of activity against HIV in vitro, and [redacted] toxicology studies testing the [redacted] in rats and dogs, IND's for AZT sponsored by BW and the NCI were approved in June 1986 for a Phase I dose escalating study in humans with AIDS and advanced ARC. The results of this study in 19 patients, which was extended to include prolonged oral dosing following an initial 2-4 weeks of [redacted] are reviewed under Uncontrolled Studies below.

In February 1986, enrollment was began in a double-blind, placebo-controlled, multicenter trial of AZT at a dose of 200 mg every 4 hours in newly diagnosed AIDS patients within 120 days of onset of first episode of Pneumocystis carinii pneumonia (PCP), and in patients with advanced ARC (manifested by significant weight loss and/or oral candida infection). All patients were required to have an absolute T-helper cell (Th) count in the peripheral blood of less than 500/mm³ and cutaneous anergy to four common recall antigens. Enrollment continued until June 30, 1986, at which time 282 patients had been entered (including one person twice). An Independent Data Safety and Monitoring Board (DSMB) was scheduled to review the data bimonthly for evidence of toxicity or efficacy of sufficient magnitude to warrant early termination of the trial. The first DSMB review occurred on August 1, 1986, at which time data through July 1, 1986 on mortality, opportunistic infections (OI's) and hematologic toxicity was examined in a blinded fashion, and the recommendation was made to continue the trial. Early in September, as the sponsor was preparing data for the scheduled October 1, 1986 review, it became apparent that there was a marked imbalance in deaths reported in the two treatment groups. More data was collected and the Data Safety and Monitoring Board was asked to meet earlier than planned. On September 18, 1986, the Board recommended that the placebo arm of the study be discontinued. At this time there was one death in the AZT group and 17 in patients assigned to placebo (9 of whom were classified as ARC patients at entry). Burroughs Wellcome followed the advice of the Board, and offered AZT recipients the option of continuing to receive AZT (at a reduced dose of 100 mg q 4 h because of concern regarding the toxicity of the 250 mg q 4 h regimen), and placebo patients were offered AZT at a dose of 200 mg q 4 h to be followed by an automatic dose reduction to 100 mg q 4 h after 4 weeks of therapy. Several weeks later the decision was made that all patients should receive 200 mg q 4 h [illegible] as tolerated and the company restored the original dose in patients who had tolerated it.

The medical and statistical report from the placebo controlled trial (Protocol 02) constitutes a summary of the pivotal and only controlled study in this NDA. The analysis includes data up through the 20th of September, at which time the placebo arm was discontinued. Data from the AZT patients who remained on drug and from the placebo patients who were begun on AZT after September 19 (Protocol CC) was not submitted with the original NDA, but the sponsor was told that the Agency would want to review important data from this study before an approval decision on the NDA was finalized. On January 12, 1987, the sponsor submitted an update on deaths and opportunistic infections (OI's) through December 23, 1987, and on February 13, 1987, the sponsor was requested to submit another update, to include information obtained in telephone calls to all of the principal investigators. This medical officer has seen desk copies of the important data, which has not yet been formally submitted to the NDA.

CONTROLLED STUDY:

As described above, the major and only controlled clinical trial supporting this application is a multicenter placebo-controlled study of one dose of AZT in carefully defined subgroups of patients with AIDS/OI and ARC (AIDS-Related Complex). This study, entitled "A Multi-Center, Placebo-Controlled Trial to Evaluate Zidothymidine (AZT) in the Treatment of Human Immunodeficiency Virus (HIV) Infections in Patients with AIDS Related Complex (ARC) or Acquired Immune Deficiency Syndrome (AIDS)," was intended to last 6 months but was prematurely discontinued on September 18, 1986, after a median duration of drug of 4 1/2 months, due to a reduction in mortality in the AZT arm compared to the group receiving placebo.

The objectives of this study, as stated in the original protocol, were 1) To evaluate the degree of safety of AZT when used to treat ARC/AIDS patients for 6 months, and 2) To evaluate the efficacy of AZT based on the following criteria: a) Clinical improvement as measured by weight gain, increased Karnofsky performance, improved CNS status, decrease in fever, and reduction in frequency and severity of severe opportunistic infections, b) Restoration of immune response as measured by reactivation of cutaneous hypersensitivity, significant and consistent increase in absolute T_4 lymphocyte counts and T_4/T_8 ratios, and increase in total lymphocyte counts, and c) Antiviral effect as measured by a reduction in the ability to detect virus-coded products (reverse transcriptase) or disappearance of virus from the blood or other body fluids. Death was not originally specified as an endpoint for efficacy analysis.

It was also stated in the original protocol that "periodic review of the data (every 2 months) will be performed during therapy by an independent Scientific Review Board." It was not specified what data would be reviewed or on what basis early termination would be considered. However, the DSMB decided before the first meeting (August 1, 1986) that death and incidence of OI's would be the efficacy parameters examined, and specified that the early stopping rules of O'Brien and Fleming would be followed in deciding at what level of significance a difference between the two treatment groups would justify premature termination of the trial.

Two categories of HIV-infected patients were eligible for this trial, as described below. Key factors in deciding upon entry criteria were 1) to include patients similar to those in whom encouraging preliminary signs of efficacy were seen in the Phase I trial, 2) to bracket as homogeneous a group as possible in terms of prognosis, and 3) to restrict entry to sick patients in whom progression could be objectively assessed according to generally accepted clinical criteria (i.e. progression from ARC to AIDS, incidence of OI's).

Patients with AIDS were limited to those who have recovered from their first episode of pneumocystis carinii pneumonia (PCP) within 90 days (no longer than 120 days after clinical diagnosis).* Patients with Kaposi's sarcoma (KS) or other malignancies were specifically excluded. Patients with ARC were required to have either significant unexplained weight loss (>10% or > 15 lbs within the previous 2 months) and/or a documented history of mucocutaneous oral candidiasis (by culture or KOH smear). One additional ARC sign or symptom was also required.

were they?

All patients, whether AIDS or ARC, were also required at entry to have a granulocyte count> 1000/mm^3, absolute Tq count < 500/mm^3, Ts/Tq ratio<1.0, cutaneous anergy to 4 standard antigens (trichophyton, tetanus toxoid, candida, and tuberculin PPD), one positive blood culture for HTLV-III within 3 months prior to entry or one pending, and positive antibody to HTLV-III. Patients were to be pre-stratified and randomized by center according to entry Tq count (< 100 or > 100/mm^3). Patients with negative blood cultures for HTLV-III at entry were to be post-stratified and analyzed separately.

were they replaced?

Two hundred and sixty patients were targeted for enrollment to be randomized equally between placebo and AZT. The protocol stated that patients dropping out within the first 2 months would be replaced, but did not address the issue of evaluability. Patients were to be followed as outpatients and seen weekly for the first month and biweekly thereafter.

The trial was originally planned to last 24 weeks and study one dose of AZT, 200 mg q 4 h around the clock. This frequency of administration was based on the short half-life of the drug (1 hr). No standard dose reduction criteria were specified, despite the known hematologic toxicity of the drug.

An effort was made to limit the use of concomitant medications by specifying several uniform approaches to treating the more common reasons for the use of concomitant medication in patients with AIDS and ARC (including PCP, recurrent fevers, diarrhea, oral candida, insomnia). Use of other medications was to be approved by the sponsor prior to administration. Investigators were warned against chronic use of aspirin or acetaminophen because of possible competition for glucuronidation of AZT.

Patients were to be evaluated at each visit for subjective symptoms (headache, mental acuity, malaise, fatigue, dyspnea, nausea, abdominal discomfort, loss of appetite, tremors, and lethargy) and objective signs (weight, vital signs, rash, and the presence of any infection or AIDS-related neoplasm). A limited physical examination, including assessment of lymphadenopathy, was to be performed every 4 weeks. A comprehensive physical examination was scheduled at 12 and 24 weeks. A neuropsychiatric evaluation aimed at assessing the

need records of attendance at follow up

presence and course of HTLV-III neurologic disease was scheduled every 8 weeks. Routine laboratory evaluations (hematology, chemistries and urinalysis) were scheduled at the same time as clinic visits (every week x 4, then biweekly). In addition, vitamin B_{12} and folate levels were obtained every 3 weeks, and blood for HTLV-III culture was scheduled to be obtained every 4 weeks. A urine sample at entry was to be cultured for CMV, and if positive, repeat urine cultures were to be done every 4 weeks.

Antibody determinations in serum for HTLV-III were to be performed every 4 weeks; for cytomegalovirus (CMV), Epstein Barr virus (EBV), and Hepatitis B virus (HBV) at entry and 24 weeks; and immunoglobulin levels at entry, 12 weeks, and 24 weeks.

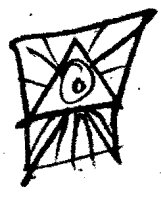
Delayed hypersensitivity skin testing was scheduled every 8 weeks, and blood for T_4 levels and T_4/T_8 ratios every 4 weeks. Serum was also to be drawn, frozen and banked at entry and every 4 weeks for measurement of alpha interferon levels and also to be stored for possible future analysis of other parameters.

Peak and trough serum levels of AZT were scheduled to be obtained at 4 weeks, 12 weeks, and 24 weeks at selected centers (not specified in the original protocol).

A comprehensive follow-up visit was originally scheduled at week 28, four weeks off therapy.

Patients were to be removed from the study for the following reasons: 1) non-compliance, 2) voluntary withdrawal, 3) concurrent illnesses requiring the use of an additional experimental agent or an agent which causes neutropenia or significant risk of nephrotoxicity (because of concern that such an agent may potentiate the toxicity of AZT), and the use of rifampin or one of its derivatives or another drug likely to have antiretroviral activity, 4) investigator non-compliance, or 5) adverse experiences (at discretion of sponsor or investigator). Chronic therapy with "suppressive" or "prophylaxis" doses of anti-infectives was specifically prohibited.

Patient enrollment into the trial began on February 13, 1986, at the University of Miami, and ended on June 30, 1986, when the last patient was enrolled at LAC-USC Medical Center in Los Angeles. Patient enrollment was limited to 30 patients per center with the exception of the first two centers(*), and accrual at each center was to take no longer than 2 months.



The following is the list of study centers and principal investigators; in alphabetical order:

Principal Investigator		Institution
David Durack, M.D.	(13)	Duke University Medical Center, Durham, NC
*Margaret Fischl, M.D.	(43)	University of Miami, Miami, FL
Michael Gottlieb, M.D.	(24)	UCLA Medical Center, Los Angeles, CA
Michael Grieco, M.D.	(25)	St. Luke's-Roosevelt Hospital, NYC, NY
Jerome Groopman, M.D.	(21)	New England Deaconess Hospital, Boston, MA
George Jackson, M.D.	(18)	University of Illinois, Chicago, IL
Oscar Laskin, M.D.	(22)	Cornell Medical Center, NYC, NY
John Leedom, M.D.	(23)	LAC-USC Medical Center, Los Angeles, CA
Donna Mildvan, M.D.	(20)	Beth Israel Medical Center, NYC, NY
*Douglas Richman, M.D.	(32)	UCSD Medical Center, San Diego, CA
Robert Schooley, M.D.	(19)	Mass. General Hospital, Boston, MA
Paul Volberding, M.D.	(22)	UCSF Medical Center, San Francisco, CA

( ) = number of patients enrolled

investigator #10 - impropriety in his work

A computer-generated, randomized code was used to assign eligible patients to AZT or placebo. Drug assignment was randomized in blocks of four. Initially the placebo capsules, which were indistinguishable from the AZT capsules in appearance, were distinguishable in taste. This difference was corrected and the placebo capsules replaced with new ones after early reports were received of patients breaking the capsules and tasting the medication.

A centralized clinical laboratory was utilized to perform the hematologic, blood chemistry, and urinalysis testing and data tapes were sent directly to the sponsor. Clinical monitors were sent out by the sponsor to visit each center every 2-3 weeks to assure the accuracy of the data transcribed onto the case report forms (CRFs).

Clinical signs and symptoms recorded at each visit were originally restricted to a 10 item check list (severity rating 0-3). Halfway through the trial, this list was augmented to include more than 30 items often associated with AIDS or ARC. Adverse experiences, if present, and their relationship to test drug, were evaluated and recorded at each visit.

SEE CRFs changed

How were they LABELLED ?

I. Sponsor's Analyses of Placebo-Controlled Trial

The information reviewed in the combined medical/statistical report for this study includes all data collected through September 20, 1986, with the following exceptions:

- Results of interferon levels, blastogenic responses, and serologic testing were omitted (to be discussed in subsequent amendments to this report).
- Results of the neuropsychiatric testing were not submitted. This data is being analyzed outside of BW by qualified consultants at the University of Kentucky Medical Center. A preliminary analysis of the data was presented at the FDA Anti-Infective Drug Advisory Committee on January 16, 1987.
- Complete analysis of the virology data has not been completed. There were a number of problems with standardization of culture techniques, completeness of data from all centers, and interpretation of results.
- The results of serial urine CMV cultures are not complete.
- The serum levels of AZT obtained from patients on study have not been completely analyzed.

A. Sponsor's Analysis of Demographics

1) Patient Population:

Two hundred and eighty-two patients were enrolled into the Phase II study between February and June 1986, 160 of whom were AIDS patients who had recovered from their first episode of PCP diagnosed no more than 120 days prior to entry, and 122 ARC patients who had multiple clinical symptoms including significant weight loss and/or oral candidiasis. All patients, regardless of clinical diagnosis of AIDS or ARC, were pre-stratified and randomized according to pre-entry absolute T_4 counts < 100 and between 100-500/mm^3. The table below shows the breakdown in numbers of patients enrolled by clinical diagnosis and absolute T_4 count. A total of 145 patients were assigned to the AZT group and 137 to the placebo group. They were fairly evenly distributed across the four subgroups created by the two variables, clinical diagnosis (AIDS or ARC) and T_4 count $<$ or $>100/mm^3$.

Of the total 282 patients, 229 met all entry criteria both during the two-week pre-entry evaluation period and on the first day study drug was administered. Fifty-three (53) patients did not meet all of the eligibility criteria at the time of entry. Because they had met the criteria earlier in the two week pre-entry period, they were allowed to remain in the study. The differences between the pre-entry and entry evaluations consisted primarily of small changes in certain laboratory criteria.

The sponsor examined the AZT and placebo groups for baseline comparability with respect to a number of variables, as shown in the table below (means for each group presented).

Baseline Variable	AZT (N)	Placebo (N)
Age(years)	35.2 (145)	35.4 (137)
Weight(kg)	68.9 (140)	68.4 (137)
Karnofsky Score(maximum 100)	89.9 (143)	89.5 (137)
Number of symptoms(maximum 10)	2.8 (144)	3.3 (137)
Sum of Symptom Scores(maximum 30)	3.9 (144)	4.7 (137)
Days Since Diagnosis of PCP	77.5 (83)	80.5 (79)
T4 Lymphocyte Count(average of pre-entry and entry values)	120.9 (145)	121.0 (136)
Sex: Male	139	130
Female	6	7

The sponsor claims that the only statistically significant difference between the two treatment groups was in the mean number of days since diagnosis of PCP in the AIDS patients (P=0.0391); 77.5 days for the AZT group and 86.6 days for the placebo group. They state that this difference was not felt to be clinically significant since statistical analyses of mortality and the development of opportunistic infections examined the impact of time since diagnosis of PCP and no significant effect was observed.

The sponsor also analyzed summary statistics of the demographic and baseline comparability variables by month of accrual and by study centers and found no significant difference between the treatment groups with respect to rate or time of accrual.

2) Patient Accountability:

Of the 282 patients originally enrolled into the study, 194 were active participants when it was terminated by the sponsor in September 1986, 27 had completed the protocol, and 61 were withdrawn prior to its termination (21 from the AZT group and 40 from the placebo group, including deaths).

The primary reasons for patient withdrawal are summarized by the sponsor in the table below:

Reasons for Treatment Discontinuation

	AZT	Placebo
Non-medical:		
Patient request[1]	4	11
Non-compliance	1	0
Protocol violation	2	1
Medical:		
Death of Patient (while receiving study medication)	0	10
Opportunistic infection[2]	7	8
Progressive Kaposi's Sarcoma	0	1
Other infections	2	2
Generalized debilitation[3]	0	7
Potential Adverse Experiences	4	0
Allergic Reaction/Patient Request	1	0
	21	40

[1]Note: one of these patients (placebo) later died
[2]Note: four of these patients (1 AZT, 3 placebo) later died
[3]Note: five of these patients (all placebo) later died

It should be noted that patients were not required to withdraw from the study if they acquired an infection or Kaposi's sarcoma unless the infection or malignancy required treatment with other experimental drugs or those that were prohibited by the protocol due to the potential for adverse drug interactions.

Four AZT and no placebo patients withdrew from the study for possible drug related adverse experiences including intractable nausea in one patient and hematologic abnormalities in three (one of which was complicated by treatment of a concurrent OI).

There were no significant differences in the percent of patients in each treatment group remaining in the study at the end of each 4-week period, as can be seen in the sponsor's table below.

Number of Patients (%) Completing N Weeks of Study

Duration (Weeks)	AZT	%	Placebo	%
4	132	(91)	127	(93)
8	129	(89)	119	(87)
12	123	(85)	112	(82)
16	80	(55)	72	(53)
20	44	(30)	39	(28)
24	9*	(6)	6*	(4)

* These 15 patients completed the study. An additional 12 patients were considered to have completed the study at week 23. Therefore, the total number of patients completing the protocol is 27 or 9.5%.

B. Sponsor's Analysis of Efficacy

The major efficacy parameters analyzed in the study were mortality and the development of opportunistic infections or neoplasms associated with AIDS. Patients were also monitored for other measures of efficacy, including changes in HIV associated symptoms, performance status, and body weight. Immune status was followed by changes in number of T_4 lymphocytes and delayed cutaneous hypersensitivity testing. An attempt was also made to ascertain the effect of treatment on the ability to recover virus from the blood via lymphocyte co-cultivation and measurement of reverse transcriptase activity.

The analyses of efficacy were performed on data available through the third week of September, 1986.

1) Mortality

Only one AZT recipient died during the trial, nine days after withdrawal due to the development of a second OI during the trial, disseminated cryptococcosis, for which he refused specific therapy. By contrast, 19 placebo recipients died during the trial. The difference in mortality is highly significant ($P < 0.001$) by Cox's regression model (please see Statistical Review of this NDA).

The sponsor analyzed the mortality statistics in several other ways, including comparing the probability of 24 week survival for all patients, and for AIDS and ARC patients separately, as shown below.

Table 3.1-1
Analysis of Overall Mortality

Patient Group		24 Week Survival Probability	P-Value
ALL Patients	AZT	0.98	<0.001
	Placebo	0.78	
AIDS Patients	AZT	0.96	<0.001
	Placebo	0.76	
ARC Patients	AZT	1.00	0.016
	Placebo	0.81	

The data were re-analyzed excluding the deaths of 2 ARC patients in the placebo group which occurred within the first three weeks of the study, and the results are shown in the table below.

Table 3.1-2
Analysis of Mortality After Excluding 2 Early Deaths (Both Deaths Occurred in ARC Patients)

Patient Group		24 Week Survival Probability	P-Value
ALL Patient	AZT	0.98	<0.001
	Placebo	0.79	
AIDS Patients	AZT	0.96	<0.001
	Placebo	0.74	
ARC Patients	AZT	1.00	0.046
	Placebo	0.83	

As can be seen, the differences between treatment groups remained statistically significant, although the P-value is just under 0.05 for the ARC patients.

At this reviewer's request, the sponsor also analyzed the mortality data according to the original randomization strata, i.e. T_4 counts above and below $100/mm^3$. Revised tables showing the probability of 24 week survival for the following four subgroups (AIDS, ARC, T_4 100 at entry and T_4 100 at entry) for all deaths and excluding the two early deaths were submitted by the sponsor on January 12, 1987 and are reproduced below.

Table 2.1-1

Probability of 24 Week Survival

T4 Count	Treatment	Probability	P-Value
Low	AZT	0.86	<0.001
	Placebo	0.70	
AIDS*	AZT	0.83	<0.001
	Placebo	0.76	
High	AZT	1.00	0.023
	Placebo	0.91	
ARC*	AZT	1.00	0.016
	Placebo	0.91	

*from original analysis (Doc. No. THRS03/0045)

Table 2.1-2

Probability of 24 Week Survival Excluding 2 Early Deaths

T4 Count	Treatment	Probability	P-Value
Low	AZT	0.86	<0.001
	Placebo	0.71	
AIDS*	AZT	0.83	<0.001
	Placebo	0.74	
High	AZT	1.00	0.051
	Placebo	0.93	
ARC*	AZT	1.00	0.045
	Placebo	0.93	

*from original analysis (Doc. No. THRS03/0045)

When the two early deaths are excluded, there is not a statistically significant difference between the treatment groups in mortality for patients stratified to the group entry $T_4 > 100/mm^3$.

No diff

Most of the deaths in the study (17/20) were attributed to opportunistic infections secondary to AIDS, as can be seen from the following table.

Table 3.1-3
Causes of Death

Patient Number	Date Medication Discontinued	Date of Death	Cause
Opportunistic Infections			
102	4/28/86	5/1/86	Suspected MAI or CMV
* 105	6/20/86	8/1/86	CMV ?
112	7/21/86	9/17/86	Suspected TB or CMV
113*	9/1/86	9/10/86	Cryptococcosis
214	9/20/86	9/22/86	Pneumonia
307	8/20/86	9/12/86	PCP
412	5/13/86	5/16/86	Cryptococcosis
464	7/2/86	7/2/86	Toxoplasmosis
552	8/11/86	8/25/86	PCP
604	8/20/86	8/20/86	Pneumonia ?
607	9/9/86	9/12/86	Pneumonia ?
703	7/28/86	8/28/86	MAI
803	6/17/86	6/26/86	Toxoplasmosis
814	9/20/86	9/20/86	PCP
1001	4/26/86	8/15/86	PCP
1009	6/25/86	8/20/86	MAI
1153	8/7/86	8/7/86	Cryptococcosis and Toxoplasmosis
Other			
208	6/11/86	9/11/86	Pulmonary edema
452	6/23/86	6/24/86	AIDS
901	5/1/86	7/15/86	Lymphoma

*AZT recipient
CMV = cytomegalovirus; MAI = Mycobacterium avium-intracellulare; PCP = Pneumocystis carinii pneumonia;
TB = Tuberculosis

Of the twenty deaths, ten occurred in patients who were still taking their study medication. Eleven patients, including the one AZT recipient, had withdrawn from the study.

Many of the causes of death listed in this table were not verified in the Case Report Forms submitted to the NDA.

2) Opportunistic Infections

The sponsor decided after the trial was underway that for the purpose of this study, opportunistic infections were those which the Centers for Disease Control have determined to be diagnostic for AIDS, including the following:

Pneumocystis carinii pneumonia
Chronic cryptosporidiosis
Toxoplasmosis
Extraintestinal strongyloidiasis
Isosporiasis
Candidiasis (esophageal, bronchial, or pulmonary)
Cryptococcosis
Histoplasmosis
Mycobacterial infection with Mycobacterium avium complex or M. kansasii
Cytomegalovirus infection (pneumonitis or colitis)
Chronic mucocutaneous or disseminated herpes simplex virus infection
Progressive multifocal leukoencephalopathy

According to the sponsor, twenty-four AZT recipients and 45 placebo recipients developed an opportunistic infection while they were on study medication. One AZT recipient and five placebo recipients each acquired two OI's.

There was a significant difference ($p < 0.001$) between AZT recipients and placebo recipients in the probability of acquiring an opportunistic infection within 24 weeks, when all patients were included, as can be seen in the table below.

Table 3.2-1
Probability of Acquiring an Opportunistic Infection Within 24 Weeks

Patient Group		Probability of Developing an Opportunistic Infection Within 24 Weeks	P-Value
All Patients	AZT	0.23	< 0.001
	Placebo	0.43	
[illegible] Patients	AZT	0.33	0.004
	Placebo	0.54	
ARC Patients	AZT	0.09	0.066
	Placebo	0.30	

The difference remained highly significant when AIDS patients only were analyzed, but lost statistical significance in ARC patients alone.

For AIDS patients, the time since diagnosis of PCP prior to entry was examined and found to have no significant effect on the probability of developing an OI. On the other hand, absolute number of T_4 cells at entry was significantly correlated with probability of developing an OI in both AIDS and ARC patients.

The probability of developing an OI within 24 weeks was also determined excluding any infections that occurred in a patient within 6 weeks of start of study medication. (This particular analysis was not specified prospectively). The sponsor claims that "this analysis was performed to avoid the possibility of undue bias against the placebo group on the assumption that opportunistic infections which developed within the first 6 weeks of the study may have been ongoing but undetected at entry."

* It is not clear why the sponsor chose 6 weeks as the period where this "undue bias against the placebo group" might exist except that no opportunistic infections occurred in ARC patients who had received AZT for at least 6 weeks. The results of this analysis are presented below.

Table 3.2-2
Probability of Acquiring an Opportunistic Infection Within 24 Weeks (Excludes Opportunistic Infections Acquired Within Six Weeks of Entry into the Study)

Patient Group		Probability of Developing an Opportunistic Infection Within 24 Weeks	P-Value
ALL Patient	AZT	0.16	< 0.001
	Placebo	0.26	
AIDS Patients	AZT	0.30	0.002
	Placebo	0.45	
ARC Patients	AZT	0.00	0.002
	Placebo	0.25	

Base

It can be seen that the difference between the treatment groups in the probability of developing an opportunistic infection at 24 weeks becomes quite significant (p=0.002) for ARC patients when OI's diagnosed within the first 6 weeks are excluded. By excluding these early OI's, the sponsor in fact makes the analysis look much more favorable for AZT.

In conjunction with the expanded mortality analyses (i.e. to include subgrouping by the original stratification variables, entry T_4 counts greater than or less than 100/mm^3), this reviewer requested the sponsor to analyze the OI data by T_4 high and low subgroups. These analyses were submitted on January 12, 1987 and are reproduced in the tables below.

Table 2.1-3
Probability of Acquiring an OI within 24 Weeks

T4 Count	Treatment	Probability	P-Value
Low	AZT	0.30	0.032
	Placebo	0.53	
AIDS*	AZT	0.33	0.004
	Placebo	0.54	
High	AZT	0.23	0.014
	Placebo	0.39	
ARC*	AZT	0.07	0.005
	Placebo	0.20	

*from original analysis

Table 2.1-4
Probability of Acquiring an OI within 24 Weeks
(Excluding Infections Occurring in First 6 Weeks)

T4 Count	Treatment	Probability	P-Value
Low	AZT	0.31	0.005
	Placebo	0.44	
AIDS*	AZT	0.30	0.002
	Placebo	0.45	
High	AZT	0.09	0.003
	Placebo	0.23	
ARC*	AZT	0.09	0.002
	Placebo	0.25	

*from original analysis

As can be seen, for the analysis of all OI's the p-values for the difference between treatment groups in the probability of developing an OI within 24 weeks are statistically significant for both the low T4 subgroup (p=0.022) and the high T4 subgroup (p=0.014). When OI's occurring within the first 6 weeks are excluded, the P-values are even more statistically significant and smaller for all subgroups.

The sponsor also attempted an analysis of the severity of OI's between the two treatment groups. Severity score (mild, moderate, severe, fatal) was determined by the investigator (sometimes retrospectively, as the "OI" pages of the Case Report Forms were created during the trial) without any objective guidelines as to what each category contained (except fatal). A total of 74 OI's were reported during the study, 15 of which had no severity score (in five of these instance, the infections were ongoing at time the study was terminated).

The differences in severity of OI's were analyzed for all patients, by AIDS/ARC diagnosis, and by high/low T4 count at entry, by the Mantel Haenszel method, and statistical significance was not achieved, as seen in the table below:

Table 3.2-3
Severity of Worst Opportunistic Infection

				Worst Severity				
Diagnosis	Entry T4	Trt.	N	Mild	Moderate	Severe	Fatal	P-values**
AIDS		AZT	16	2	8	6	0	.064
		PCO	27	3	14	6	4	
ARC		AZT	5	1	4	0	0	.053
		PCO	11	1	4	4	2	
All Patients	Low	AZT	18	3	11	4	0	.172
		PCO	31	3	15	9	3	
	High	AZT	3	0	1	2	0	.807
		PCO	7	1	2	1	3	
Overall		AZT	21	3	12	6	0	.174
		PCO	33	4	13	10	6	

* Fatalities reported herein do not include an additional 11 deaths attributed to OI which occurred after patients withdrew from the study.
**Mantel Haenszel method.

However, trends favored AZT recipients for lesser severity of OI's. The sponsor notes that this analysis underestimates the difference in severity of infections between treatment groups because it does not reflect the number of fatal infections that occurred in patients who withdrew from the trial, i.e. 10 placebo recipients. (On the other hand, it could be argued that to include fatal infections in the anlysis of severity of OI's unfairly biases against the placebo group by "counting" fatal infections twice in the analyses of the major efficacy endpoints, i.e. both in the mortality analyses and in the "severity of OI's" analyses). The sponsor adds that a subsequent analysis of severity of OI's will be completed to take into account additional data from such patients.

3) Kaposi's Sarcoma

Sixteen patients developed Kaposi's sarcoma (KS) during the course of the study (10 placebo recipients and 6 AZT), and there is not a statistically significant difference between the treatment groups. In addition to the cases of KS, one placebo patient developed non-Hodgkin's lymphoma and later died of this malignancy.

4) Karnofsky Performance Scores

The Karnofsky Performance Scale was utilized at each visit to measure the functional capability of patients which thus reflects quality of life. Patients were required to have a performance score of $\geq$ 70 to enter the study on the scoring system outlined below.

KARNOFSKY PERFORMANCE SCALE

Able to carry on normal activity; no special care is needed.	100 Normal; no complaints; no evidence of disease
	90 Able to carry on normal activity; minor signs or symptoms of disease
	80 Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; a varying amount of assistance is needed	70 Cares for self; unable to normal activity or to do active work
	60 Requires occasional assistance but is able to care for most of his needs
	50 Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40 Disabled; requires special care and assistance
	30 Severely disabled; hospitalization is indicated although death not imminent
	20 Very sick; hospitalization necessary; active supportive treatment is necessary
	10 Moribund; fatal processes progression rapidly
	0 Dead

According to the sponsor, there were no entry violations on this criterion. No differences existed between AZT and placebo groups at baseline (AZT: median score = 90; mean score = 89.9. Placebo: median score = 90; mean score = 89.5). Change in Karnofsky scores at four week intervals are summarized in the table below:

Table 3.3-2
Change of Karnofsky Scores From Baseline

		AZT			Placebo			
			Change from Baseline			Change from Baseline		
Group	Week	N	Median	Mean	N	Median	Mean	P-Value*
All Patients	4	132	0.0	-0.3	130	0.0	-2.2	0.0457
	8	130	0.0	+0.9	120	0.0	-3.8	0.0006
	12	125	0.0	+1.3	109	0.0	-5.2	0.0001
	16	90	0.0	-0.3	80	0.0	-5.6	0.0787
	20	53	0.0	-0.5	44	0.0	-5.0	0.0791
	24	25	0.0	-2.0	16	0.0	-8.1	0.5232
AIDS Patients	4	77	0.0	+0.4	74	0.0	-1.9	0.0957
	8	75	0.0	+1.1	68	0.0	-3.9	0.0083
	12	73	0.0	+1.6	58	0.0	-5.9	0.0006
	16	50	0.0	-0.5	39	0.0	-4.6	0.2192
	20	33	0.0	-0.6	20	0.0	-5.5	0.2625
	24	13	-10.0	-3.1	6	-5.0	-5.0	0.6453
Non-AIDS Patients	4	55	0.0	-1.3	56	0.0	-2.7	0.3003
	8	55	0.0	+0.5	52	0.0	-3.7	0.0457
	12	52	0.0	+0.9	51	0.0	-4.3	0.0700
	16	40	0.0	0.0	41	0.0	-6.6	0.2068
	20	25	0.0	-0.4	24	0.0	-4.6	0.1679
	24	12	0.0	-0.8	10	0.0	-10.0	0.6555
High T_4's	4	50	0.0	-1.5	45	0.0	-0.9	0.8827
	8	50	0.0	-0.8	42	0.0	-3.0	0.4125
	12	48	0.0	0.0	40	0.0	-1.6	0.6707
	16	39	0.0	-1.8	32	0.0	-0.5	0.2761
	20	24	0.0	-2.1	20	0.0	-3.0	0.7895
	24	11	0.0	-2.7	8	0.0	-2.5	0.6088
Low T_4's	4	82	0.0	+0.4	85	0.0	-2.9	0.0173
	8	80	0.0	+1.9	78	0.0	-4.2	0.0004
	12	77	0.0	+2.1	69	0.0	-7.2	0.0001
	16	51	0.0	+0.8	48	-5.0	-9.1	0.0023
	20	34	0.0	+0.6	24	-5.0	-6.7	0.0449
	24	14	-5.0	-1.4	8	-15.0	-13.8	0.1553

*Measured by Wilcoxon's Rank Sum Test

According to the sponsor, "Since most patients entered the study with near normal performance capacity, substantial improvement of baseline scores was not expected. Overall, significant differences in change from baseline between the drug and placebo group can be observed as early as week 4. At weeks 8 and 12, the degree of significance increases. The differences seen are accounted for by the progressive deterioration of placebo patients. AIDS patients and those with low T_4 cell counts at entry appear more likely to demonstrate benefit from AZT treatment."

The sponsor goes on to note that a confounding factor in the interpretation of this analysis is that Karnofsky scores were generally recorded only when the patient was ambulatory and reported to the clinic for a scheduled visit. Data retrieval from hospitalized or otherwise incapacitated patients was extremely limited. In addition, clinical evaluations were not conducted in the event of death, so the resulting zero (0) performance score was not recorded on the case report form.

5) Body Weight

The sponsor states that "One of the clinical manifestations of HIV infection is a wasting syndrome which can produce significant losses in body weight and contributes to morbidity and mortality." Body weights of patients entered into this study were measured at entry and at each clinic visit. Entry weights for AZT and placebo recipients were comparable.

Changes in weight recorded at four-week intervals are summarized in the table below.

Table 3.3-3

Change in Patients Weight From Entry

Group	Week	AZT N	AZT Change from Baseline (kg) Median	AZT Mean	Placebo N	Placebo Change from Baseline (kg) Median	Placebo Mean	P-Value*
All Patients	4	126	+0.5	+0.5	126	+0.0	-0.1	0.0473
	8	125	+1.3	+1.5	117	+0.2	-0.2	0.0006
	12	120	+1.7	+1.9	106	-0.5	-0.9	0.0001
	16	85	+1.5	+2.0	77	-0.9	-1.3	0.0001
	20	56	+1.4	+1.6	43	-0.3	-0.2	0.0095
	24	25	+1.6	+1.5	15	-0.9	-2.6	0.1069
AIDS Patients	4	75	+0.5	+0.6	73	0.0	0.0	0.1635
	8	73	+1.4	+1.7	66	+0.2	-0.1	0.0019
	12	71	+2.0	+2.5	55	-0.4	+2.2	0.0001
	16	48	+2.0	+2.2	38	-0.9	-1.3	0.0002
	20	31	+1.9	+1.6	19	+0.2	-0.2	0.0692
	24	13	+1.7	+1.9	6	-2.1	-3.5	0.0351
ARC Patients	4	51	+0.5	+0.3	53	0.0	-0.1	0.1505
	8	52	+0.9	+1.2	51	+0.1	-0.3	0.1007
	12	49	+1.1	+1.0	51	-0.8	-0.5	0.0029
	16	37	+1.0	+1.8	39	-0.9	-1.2	0.0012
	20	25	+1.4	+1.6	24	-0.3	-0.3	0.2711
	24	12	+0.3	+1.0	9	0.0	-2.1	0.7417
High T's	4	48	+0.5	+0.0	44	0.0	+0.1	0.4976
	8	47	+1.0	+1.0	40	+0.9	+0.4	0.6496
	12	44	+1.2	+0.6	40	+0.3	+0.7	0.1771
	16	36	+1.1	+1.5	32	0.0	+0.1	0.0487
	20	24	+1.1	+1.2	20	+0.5	+1.4	0.9288
	24	11	+0.0	+0.1	8	+0.1	-0.1	0.7320
Low T's	4	8	+0.7	+0.8	82	0.0	-0.1	0.0523
	8	78	+1.4	+1.8	77	0.0	-0.5	0.0001
	12	76	+2.1	+2.6	66	-1.2	+1.0	0.0001
	16	49	+2.0	+2.3	45	-2.2	-2.3	0.0001
	20	32	+2.2	+1.9	23	-1.1	-1.6	0.0058
	24	14	+2.7	+2.6	7	-3.0	-5.5	0.0100

*Measured by Wilcoxon's Rank Sum Test

According to the sponsor, "Overall, AZT recipients tended to gain weight during the study while patients receiving placebo lost weight. Statistically significant differences between the two groups were first observed at week 4 (p=0.0473) and weight differences became greater throughout the study .... As was the case with Karnofsky performance scores, weights were measured only from ambulatory patients who reported for their scheduled visit .... Analyses using 'last observation carried forward' methods will allow data from patients dropped from the study to be incorporated into subsequent time points in the study." -The

sponsor notes that patients with AIDS and those with low entry T4 counts demonstrated the greatest difference in weight change between the drug and placebo treated groups. "Each group, however, (AIDS, ARC, high T4's and low T4's) treated with AZT experienced gains in weight."

6) AIDS-Related Symptom Scores

At entry and at each visit during the study, clinical evaluations were performed to determine the presence and severity of 10 subjective symptoms often associated with HIV infection. These were malaise, fatigue, headache, nausea, loss of appetite, tremors, lethargy, abdominal discomfort, dyspnea, and loss of mental acuity. No significant differences were present at entry between treatment groups.

Approximately halfway through the study the number of symptoms collected during the clinical evaluation was increased to a total of 33. Since these additional symptoms were not evaluated at study entry, analyses for changes from baseline were not possible. Similar to the analyses of weight and Karnofsky performance status, data was collected largely from ambulatory, nonhospitalized patients. This created a non-random bias by excluding data from sick or dead patients. The sponsor's analysis of change in the number of symptoms is presented in the table below.

Table 3.3-4

Change in Number of Symptoms From Entry

		AZT			Placebo			
			Change from Baseline (kg)			Change from Baseline (kg)		
Group	Week	N	Median	Mean	N	Median	Mean	P-Value*
All Patients	4	134	0.0	-0.1	130	0.0	+0.1	0.2399
	8	131	-1.0	-0.8	120	0.0	+0.1	0.0033
	12	126	-1.0	-0.7	110	0.0	+0.0	0.0277
	16	90	0.0	-0.7	80	0.0	-0.2	0.0326
	20	63	0.0	-0.5	45	0.0	-0.2	0.5278
	24	25	1.0	-0.7	16	-0.5	+0.1	0.4755
AIDS Patients	4	77	0.0	+0.1	74	0.0	+0.5	0.1703
	8	75	-1.0	-0.7	68	0.0	+0.7	0.0022
	12	73	-1.0	-0.6	60	0.0	+0.8	0.0042
	16	50	0.0	-0.5	39	0.0	+1.2	0.0131
	20	33	0.0	0.0	20	+0.5	+1.0	0.2693
	24	13	0.0	+0.2	6	+3.0	+3.2	0.0729
ARC Patients	4	57	-0.5	-0.3	56	0.0	-0.4	0.8355
	8	56	-1.0	-0.9	52	-0.5	-0.6	0.5252
	12	53	-1.0	-0.9	50	0.0	-0.9	0.9369
	16	40	-1.0	-1.0	41	-1.0	-0.7	0.5323
	20	25	-1.0	-1.1	25	-1.0	-1.1	0.8258
	24	12	-2.0	-1.8	10	-2.5	-1.7	0.5063
High T_4's	4	51	0.0	0.3	45	0.0	-0.4	0.4690
	8	50	0.0	-0.2	42	-0.5	-0.5	0.7779
	12	48	-1.0	-0.6	40	0.0	-0.7	0.8669
	16	39	0.0	-0.5	32	0.0	-0.8	0.8205
	20	24	0.0	-0.7	20	-0.5	-1.2	0.5470
	24	11	-2.0	-1.6	8	-3.0	-2.5	0.6589
Low T_4's	4	83	0.0	-0.3	85	0.0	+0.4	0.0435
	8	81	-1.0	-1.1	78	0.0	+0.5	0.0003
	12	78	-1.0	-0.8	70	0.0	+0.5	0.0037
	16	51	-1.0	-0.9	43	0.0	+0.9	0.0040
	20	34	0.0	-0.3	25	0.0	+0.7	0.1715
	24	14	-0.5	-0.0	8	+2.5	+2.8	0.1598

*Measured by Wilcoxon's Rank Sum Test

The sponsor states that overall, the reporting rate of symptoms remained fairly constant for placebo recipients, whereas patients receiving AZT experienced significantly fewer symptoms by week 8 of the study. AIDS patients in the placebo group were more likely to develop additional symptoms over time whereas ARC patients in the placebo group actually reported slightly fewer complaints over time based on this method of analysis.

The symptoms were weighted by severity (0 = none, 1 = mild, 2 = moderate, 3 = severe) and the number for each patient was added to calculate a "Sum of Symptoms" score.

Table 3.3-5

Change in Summation of Symptoms From Entry

		AZT			Placebo			
			Change from Baseline (kg)			Change from Baseline (kg)		
Group	Week	N	Median	Mean	N	Median	Mean	P-Value*
All Patients	4	133	0.0	-0.2	130	0.0	+0.2	0.1783
	8	131	-1.0	-1.1	120	0.0	+0.4	0.0270
	12	125	-1.0	-1.0	110	0.0	+0.6	0.0092
	16	90	0.0	-0.5	80	0.0	+0.6	0.1420
	20	53	-0.5	-0.4	45	0.0	+0.3	0.3301
	24	25	-1.0	-0.9	15	-0.5	+0.1	0.3532
AIDS Patients	4	77	0.0	+0.2	74	+0.5	+0.7	0.3523
	8	75	-1.0	-1.0	68	0.0	+1.5	0.0082
	12	73	-1.0	-0.7	60	1.0	+2.3	0.0009
	16	50	0.0	-0.3	39	0.0	+2.4	0.0551
	20	33	+1.0	+0.4	20	+1.5	+2.5	0.2316
	24	13	+1.0	+0.5	6	+5.5	+5.3	0.1013
ARC Patients	4	56	-1.0	-0.3	56	0.0	-0.4	0.3483
	8	56	-1.0	-0.9	52	-1.0	-1.1	0.7385
	12	53	-2.0	-0.9	50	0.0	-1.4	0.8606
	16	40	-1.0	-1.0	41	-1.0	-1.0	0.8974
	20	25	-1.0	-1.1	25	-1.0	-1.4	0.8601
	24	12	-2.5	-1.9	10	-4.0	-3.0	0.8513
High T_4's	4	50	0.0	+0.5	45	0.0	-0.8	0.3179
	8	50	0.0	-0.1	42	-1.0	-0.5	0.6860
	12	48	-1.0	-0.9	40	0.0	-0.9	0.8769
	16	39	0.0	-0.4	32	0.0	-1.5	0.4999
	20	24	-1.0	-1.1	20	-0.5	-1.3	0.9280
	24	11	-3.0	-2.2	8	-4.0	-4.1	0.6240
Low T_4's	4	83	-1.0	-0.7	85	+1.0	+0.8	0.0152
	8	81	-1.0	-1.8	78	0.0	+0.8	0.0021
	12	78	-1.0	-1.0	70	+1.0	+1.4	0.0016
	16	51	-1.0	-0.6	48	+0.5	+2.1	0.0135
	20	34	0.0	-0.0	25	+3.0	+1.6	0.1896
	24	14	-0.5	+0.1	8	+6.0	+4.4	0.0864

*Measured by Wilcoxon's Rank Sum Test

Results were similar to the previously presented analysis which examined change in number of symptoms from entry. Again, "patients with AIDS or those with low T4 cell counts at entry appear to have gained the most benefit from AZT therapy."

7) Immunology:

Several measures of immune status were tested prior to study entry and at various times after initiation of treatment. The sponsor has analyzed the results of serial T_4 (T-helper/inducer) cell counts and delayed cutaneous hypersensitivity testing.

T-lymphocyte subsets were measured twice prior to entry, at entry, and then every 4 weeks during the study. Patients were randomized to receive AZT or placebo in blocks based on the latest available pre-entry T_4 count (greater than or less than 100 cells/mm^3). In some cases this classification differed from what the block assignment would have been if all three pre-entry values had been available and the average used to stratify the patient.

As reflected in Table 3.4-1 on the following two pages, "changes in T_4 counts were strikingly different between the AZT and placebo recipients at weeks 4, 8, 12, 16, and 20 by Wilcoxon's Rank Sum analyses ($p < 0.001$)."

Table 3.4-1
T_4 Cell Counts By Week of Study

Group	Week	AZT N	AZT Actual Counts Mean	AZT Actual Counts Median	AZT Change from Baseline* Mean	AZT Change from Baseline* Median	Placebo N	Placebo Actual Counts Mean	Placebo Actual Counts Median	Placebo Change from Baseline* Mean	Placebo Change from Baseline* Median	P Value°
All Patients	Baseline	160	77.0	120.0	-	-	160	71.1	121.0	-	-	-
	Week 4	103	101.0	152.0	+20.0	+50.5	119	66.1	117.5	-11.2	-4.0	<0.0001
	Week 8	103	100.0	108.0	+31.7	+42.0	103	57.5	107.5	-12.7	-20.3	<0.0001
	Week 12	110	112.0	103.1	+21.2	+37.4	103	53.0	103.3	-17.0	-25.3	<0.0001
	Week 16	82	117.5	103.5	+10.2	+24.5	74	70.1	120.7	-13.2	-24.7	<0.0001
	Week 20	45	50.0	167.0	+2.7	+33.0	58	43.6	114.3	-20.9	-20.7	0.0031
	Week 24	19	101.0	107.4	-0.6	+12.0	14	74.5	101.9	-20.1	-11.7	0.0033
IVDU Patients	Baseline	85	84.0	65.0	-	-	75	49.0	77.0	-	-	-
	Week 4	60	103.0	151.0	+60.5	+83.5	63	30.5	60.3	-9.2	-2.3	<0.0001
	Week 8	72	93.0	103.4	+39.0	+50.6	69	43.1	64.4	-9.2	-16.7	<0.0001
	Week 12	67	63.0	105.7	+105.7	+35.7	56	32.7	55.8	-13.9	-25.8	<0.0001
	Week 16	44	43.0	81.0	+21.0	+10.4	30	20.0	60.2	-16.7	-27.5	0.0022
	Week 20	23	43.0	64.7	-6.0	+6.0	14	32.0	47.3	-23.8	-23.5	0.0344
	Week 24	8	10.5	81.5	+15.0	-9.9	5	20.0	34.0	-33.7	-60.3	0.0040
MSC Patients	Baseline	63	160.0	193.3	-	-	61	123.0	175.1	-	-	-
	Week 4	54	251.0	257.9	+59.0	+51.7	51	154.0	122.7	-13.3	-3.4	0.0002
	Week 8	54	204.5	222.4	+13.7	+22.5	43	114.5	161.5	-23.3	-25.0	0.0023
	Week 12	43	277.5	224.0	+52.0	+30.4	47	93.0	154.3	-30.5	-26.9	0.0002
	Week 16	30	209.0	209.7	+24.5	+40.3	30	157.5	173.0	-31.5	-22.0	0.0005
	Week 20	20	240.0	207.0	+55.5	+67.5	22	103.0	156.9	-27.0	-15.7	0.0012
	Week 24	11	217.0	262.6	+23.7	+20.5	9	154.0	232.0	-11.3	+15.3	0.7363

*mean and median of each patient's change from their baseline value
°as generated by stratified Wilcoxon's Rank Sum analysis

Table 3.2-1 (cont.)
T4 Cell Count By Week of Study

Group	Week	AST N	AST Actual Counts (Mean)	AST Actual Counts (Median)	AST Change from Baseline* (Mean)	AST Change from Baseline* (Median)	Placebo N	Placebo Actual Counts (Mean)	Placebo Actual Counts (Median)	Placebo Change from Baseline* (Mean)	Placebo Change from Baseline* (Median)	p Value@
High T4	Baseline	53	224.3	240.0	-	-	47	233.0	253.0	-	-	-
	Week 4	43	313.0	315.4	+71.0	+61.1	44	201.3	223.0	-13.5	-10.7	0.0014
	Week 8	43	274.8	283.4	+35.3	+41.2	30	209.1	220.4	-23.3	-47.2	0.0003
	Week 12	43	283.0	283.4	+50.3	+37.0	30	187.0	215.0	-43.3	-47.4	0.0000
	Week 16	33	283.3	300.1	+20.9	+59.0	31	183.5	231.5	-45.3	-41.4	0.0004
	Week 20	19	300.0	303.5	+50.7	+57.3	15	183.0	237.3	-35.7	-22.3	0.0003
	Week 24	11	217.0	284.3	+38.7	+21.3	8	220.5	275.5	-45.8	+0.7	0.4419
Low T4	Baseline	53	47.3	-	-	-	69	33.3	49.2	-	-	-
	Week 4	75	108.0	123.3	+51.1	+74.9	75	33.9	49.4	-8.9	-1.6	<0.0001
	Week 8	70	74.0	90.4	+23.0	+40.5	70	23.9	45.3	-9.9	-5.5	<0.0001
	Week 12	70	60.5	83.6	+15.3	+37.3	64	25.0	33.0	-11.7	-13.5	<0.0001
	Week 16	43	41.5	65.4	+4.3	+12.5	43	26.2	40.9	-16.7	-12.6	0.0016
	Week 20	23	43.7	68.1	+1.7	+15.0	21	20.7	33.5	-21.7	-19.2	0.0031
	Week 24	8	16.0	47.9	-12.1	+1.4	6	6.5	10.3	-29.1	-23.2	0.1005

*mean and median of each patient's change from their baseline value
@as generated by stratified Wilcoxon's Rank Sum analysis

The sponsor notes that "A gradual decline after an initial sharp increase in the number of T_4 cells was observed overall in AIDS patients receiving AZT. This phenomenon appears to coincide with development of neutropenia. Table 3.4-2 below compares T_4 counts of patients who experienced neutropenia (< 750 cells/mm^3) to those who did not. Each of these cohorts of patients completed 16 weeks of the study ... the development of neutropenia appears to be associated with the AZT recipients' ability to maintain increased T_4 levels."

Table 3.4-2

T_4 cell counts of all patients who did or did not develop neutropenia completing 16 weeks of treatment

Neutropenic (< 750 cells/mm³)							Not Neutropenic						
	AZT			Placebo				AZT			Placebo		
Week	N	Mean	Mean Change from Baseline	N	Mean	Mean Change from Baseline	Week	N	Mean	Mean Change from Baseline	N	Mean	Mean Change from Baseline
0	33	63.2	—	5	43.9	—	0	50	183.7	—	71	149.7	—
4	20	163.6	+75.9	4	19.1	-19.2	4	47	249.3	+65.9	67	149.4	+2.5
8	22	153.9	+40.3	4	44.2	-11.5	8	47	229.3	+51.1	62	135.3	-24.1
12	31	91.4	+15.9	4	23.6	-32.1	12	47	245.7	+53.0	68	122.1	-23.9
16	32	90.9	+14.0	5	24.0	-20.1	16	50	214.3	+30.6	69	127.7	-23.0
20	22	84.1	+0.2	1	24.0	-42.7	20	23	249.0	+65.0	35	116.3	-20.1
24	10	63.0	-23.4	0	—	—	24	9	277.8	+53.3	14	161.9	-11.7

5) Delayed Cutaneous Hypersensitivity

At entry, patients were required to be anergic to the following antigens: trichophyton, tetanus toxoid, candida, and purified protein derivative of tuberculin (PPD). A single lot of antigen was distributed among all study centers. Anergy was defined as 5 mm of induration at 48 hours. A positive response (conversion) was defined as ≥ 10 mm of induration to one or more antigens. A response was considered "marginal" if induration was 5-9 mm at 48 hours to any antigen.

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Skin testing was performed twice prior to study initiation, 7-14 days apart, and every 8 weeks thereafter. Two patients each had a positive response to one of the two pre-entry tests and are not included in the analysis of conversion. The frequency of skin test conversions is listed in the table below.

Table 3.4-3
Frequency of Skin Test Conversions*

Diag.	Treatment	Results of Skin Test			P-Value*
		Negative	Marginal	Positive	
All Patients	AZT	63	9	37	<0.001
	PCB	102	4	11	
AIDS	AZT	50	4	20	<0.001
	PCB	62	1	3	
ARC	AZT	33	5	17	0.074
	PCB	40	3	8	
High T_4 Count	AZT	25	3	21	0.018
	PCB	31	2	8	
Low T_4 Count	AZT	53	6	16	0.001
	PCB	71	2	3	

*Analyzed by Cochran-Mantel-Haenszel method

Except for the ARC subgroup, the difference between AZT and placebo groups in the frequency of skin conversions is significant.

Table 3.4-5 shows data regarding the persistence of positive skin response in patients with at least one positive response while on study. Half of the AZT patients who had a second test after a positive one lost reactivity.

Table 3.4-5
Persistence of Positive Skin Response

At Least One Test	Repeat Test	Number of Patients	
		AZT	Placebo
+	+	11	3
+	-	11	1
+	Not done	15	7
Total Positive Responses		37	11

The sponsor also prepared a table (not shown) listing skin test responses with corresponding T_4 cell counts over time and concluded that "There appears to be no general correlation between skin test reactivation and the absolute number of circulating T_4 cells".

9) Other Immunologic Tests

The sponsor states that "The results of other assays of immunologic function; i.e. circulating endogenous alpha interferon levels, in vitro blastogenic responses, and serologic testing for HIV, EBV, CMV, Hepatitis B and quantitative immunoglobulins, have not been analyzed at the time of this report."

10) Virology

The sponsor states, "AZT was selected for development as a potential therapy in AIDS ... based on its in vitro antiviral activity. Therefore, a major effort was initiated within the clinical trials program to determine whether administration of this compound could be associated with changes in recovery of HIV from treated patients. This has proven to be a difficult task because of the current lack of reliable, standardized quantitative methodology."

Blood samples were obtained at four week intervals from patients for HIV cultures. Briefly, the methodology consisted of co-culture of peripheral blood lymphocytes with phytohemagglutinin and heterologous cells permissive for HIV infection. Culture supernatant fluids were collected twice weekly to monitor virus growth in culture using a reverse transcriptase (RT) assay.

The sponsor notes that "there are several problems with this methodology. Most notably, the assay cannot directly detect virus in freshly drawn blood or other clinical samples .... The quantitative relationship of virus detected in amplified cultures (where non-replicating latent virus may have been reactivated) to the actual extent of viral replication in the patient at the time the specimen was obtained may be difficult to establish. However, at the time the placebo-controlled trial was begun, none of the retrovirologists involved felt that other methods for detection of HIV in clinical specimens had been evaluated sufficiently to replace demonstration of reverse transcriptase activity in the supernatant fluid of stimulated cells as the standard for definition of a positive culture." According to the sponsor, most of the investigators utilized experimental HIV detection techniques in parallel with the RT assay.

At a pretrial meeting of most of the virologists involved with the study on November 15, 1985, a standard method for collection of patient samples and processing of cultures was agreed upon. However, most investigators modified the culture methods. Comparable sensitivities of cultures between laboratories has not been established. According to the sponsor, because the majority of HIV culture results had not been transferred to data collection forms and incorporated into the database when the trial was terminated, virology data submitted to the NDA is limited.

HIV culture results were provided to the medical department of the sponsor by the virology centers along with the evaluation criteria to be used for results from each laboratory. All culture results were classified as positive or negative without knowledge of prior results or treatment status. The day on which cultures became positive was not recorded for this analysis.

Blood was obtained for HIV virus isolation before administration of AZT or placebo. Patients were considered virus positive if either pre-entry or entry cultures showed evidence of HIV replication. Results of baseline HIV culture status are shown in Table 3.5-1 below.

BASELINE HIV CULTURE STATUS

		Culture Results at Screen and/or Entry					
		Positive		Negative		Borderline or Missing	
		%	(n)	%	(n)	%	(n)
All Patients	AZT	57.2	(83)	30.3	(44)	12.4	(18)
	PCB	57.6	(79)	31.4	(43)	11.0	(15)
AIDS	AZT	53.1	(50)	30.2	(29)	11.5	(10)
	PCB	58.0	(42)	33.3	(25)	10.6	(8)
ARC	AZT	58.0	(33)	30.5	(16)	13.5	(8)
	PCB	54.3	(34)	33.3	(21)	11.3	(7)
High T4 at Entry	AZT	58.3	(33)	28.3	(15)	15.4	(8)
	PCB	51.0	(24)	36.2	(17)	12.8	(6)
Low T4	AZT	53.0	(54)	31.2	(29)	10.3	(10)
	PCB	61.1	(55)	28.9	(26)	10.0	(9)

The percentages of patients with positive cultures before the study were 57% and 58% for AZT and placebo patients, respectively. Rates of virus isolation varied somewhat between centers, but were similar between treatment groups within each center.

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*Two parameters were followed to determine antiviral effect: 1) change of an HIV culture from positive to negative and 2) delay in time to detect virus in culture. Data for changes in percentages of positive cultures over time for drug and placebo patients are presented in Table 3.5-2 below.

* No striking pattern of antiviral effect is seen.* --

Table 3.5-2
SUMMARY HIV VIROLOGY

Percent Positive (number)

		Entry % (n*)	Weeks on Drug 4 % (n)	8 % (n)	12 % (n)	16 % (n)	20 % (n)	24 % (n)
All Patients	AZT	57 (53)	63 (77)	60 (60)	53 (54)	55 (34)	50 (16)	63 (7)
	Placebo	53 (73)	53 (54)	50 (50)	49 (47)	50 (30)	63 (15)	75 (9)
AIDS Patients	AZT	53 (33)	67 (59)	60 (40)	62 (29)	55 (19)	50 (7)	75 (3)
	Placebo	53 (44)	53 (33)	51 (33)	49 (23)	51 (15)	70 (7)	100 (3)
ARC Patients	AZT	53 (33)	53 (33)	53 (20)	51 (15)	55 (15)	50 (3)	57 (4)
	Placebo	53 (33)	53 (33)	49 (23)	53 (22)	53 (15)	63 (3)	63 (3)
High T4 Patients	AZT	53 (33)	57 (37)	53 (24)	43 (17)	45 (12)	56 (9)	57 (4)
	Placebo	51 (24)	49 (23)	51 (21)	49 (15)	53 (15)	63 (7)	63 (5)
Low T4 Patients	AZT	53 (53)	67 (50)	63 (44)	63 (37)	62 (22)	43 (7)	75 (3)
	Placebo	62 (55)	61 (43)	59 (37)	55 (32)	43 (15)	72 (8)	0 (3)

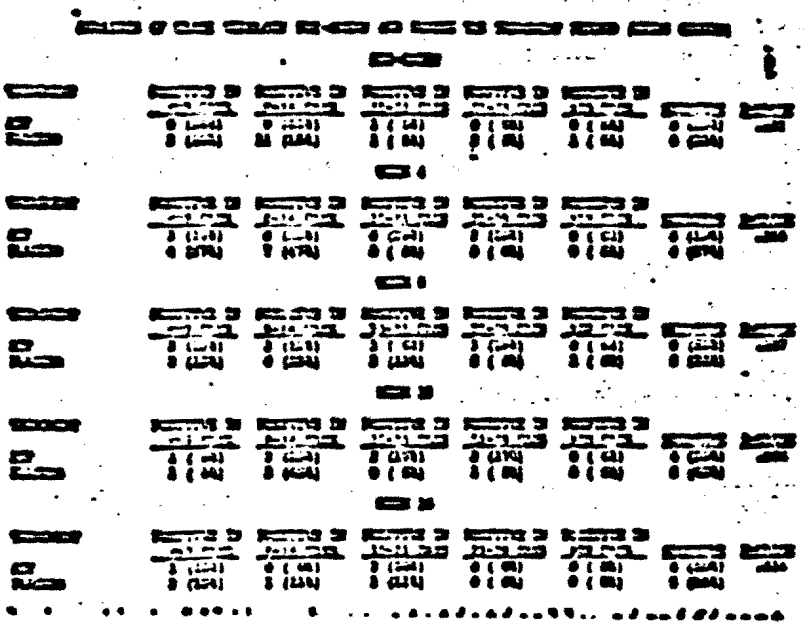
*( ) Number of patients with positive culture results

Since many patients had inconsistent recovery of virus from their lymphocytes, the data were analyzed independently for that subset of patients for whom positive cultures were documented prior to the study. Again, no changes in the percentage of patients with positive cultures were seen.

* Formal statistical analysis of the viral culture data is limited to the patients enrolled at the Miami study center which constituted the largest group who were also on study for the longest period of time(23 of the 41 patients enrolled at this center completed at least 20 weeks of blinded therapy).

HIV cultures were rated as positive or negative according to the conventions established by Dr. Parks, the virologist for the Miami center. For each positive culture, the day in culture on which HIV activity was first evident (by RT activity or detection of p24 antigen) was recorded.

The results based upon the reverse transcriptase activity in culture are presented the table below.



Seventy-one percent of AZT recipients and 75% of placebo patients had positive cultures at entry.

The sponsor concludes that "Although no statistically significant differences are documented between the two groups over the course of the study, there is a trend toward longer times to positive cultures and/or negative cultures in those patients treated with AZT. This effect is most notable at week 4 (p=.255) and week 8 (p=.167) of the study."

meaningless a statistical (sampling variation) artifact at best.

HIV cultures from the Miami center were also analyzed using the results of a p24 antigen capture radioimmunoassay to detect virus in lymphocyte culture supernatants. Again, "no statistically significant changes in the percent of positive cultures or time to detection of virus in culture were observed."

Two groups of investigators, Dr. Parks et al in Miami and Dr. Chaisson et al in San Francisco, have independently (of the sponsor) assessed potential AZT antiviral activity in patients enrolled in their respective centers using methods other than reverse transcriptase assays to detect HIV replication. Dr. Parks used a p24 antigen capture radioimmunoassay developed in his laboratory to evaluate the HIV culture results as noted above. He examined both time to positive cultures and the conversion of positive cultures to negative. The sponsor states that "A delay in time to positive cultures and an increased incidence of negative cultures was demonstrated for AZT patients individually and as a group. These apparent antiviral effects correlated with increased number of T_4 cells and improved clinical status in 'virus responders'."

The sponsor offers the following explanation as to why Dr. Parks' conclusions from the p24 antigen capture radioimmunoassay data differs from their own: "Dr. Parks' analysis includes different numbers of cultures for each patient and evaluates positive cultures by determining the amount of p24 antigen detected quantitatively over time. This may explain the discrepancy in demonstration of antiviral activity."

Dr. Chaisson used an Abbott Laboratories ELISA kit to directly detect HIV p24 antigen in serum and "showed that levels of this protein in AZT patients remained relatively constant or decreased over the course of therapy, while those of placebo recipients increased. The difference in mean HIV antigen levels at 16 weeks was highly significant ($p < 0.003$) and persisted at 20 weeks ($p < 0.005$)."

B-W doesn't like results.

The sponsor concludes that the virology data presented are limited and the results inconclusive based "partially upon the current incomplete analysis and also probably the limitations of the culture method used."

C. Sponsor's Analysis of Safety

1) Clinical Adverse Experiences

Each reported adverse experience was matched to a standardized term (COSTART) from a dictionary of preferred adverse experience terms and categorized under a specific body system. Abnormal laboratory values are analyzed and discussed later.

Analysis of the maximum recorded severity of adverse experiences was done by the Cochran-Mantel-Haenszel method for all patients and stratified by diagnosis and entry T_4 count. A similar analysis was done excluding reports considered definitely not drug related and excluding seven reports for which causal relationship to drug was unknown.

According to the sponsor, 221 of the 282 patients enrolled in the study reported at least one adverse experience for an incidence rate of 78%. (AZT = 122/145 = 84%; PCB = 99/137 = 72%). "Adverse experience reporting often included events which were in reality clinical manifestations of HIV infection. This is apparent by reviewing the similar frequency of most events reported by patients receiving either AZT or placebo .... In the analysis of all patients, nausea, myalgia, and insomnia were the only adverse experiences which were reported at a significantly higher frequency in AZT recipients than in placebo recipients." These three complaints are analyzed by severity and AIDS/ARC subgroups in Table 4.1-1 below.

How ascertain

Subsequent Experience w/ intolerance differs

N = all (N=282)

Total Recipients at Beginning of Study yet only 15 finished all 24 weeks

Table 4.1-1

Summary of Statistically Significant Clinical Adverse Experiences Occurring More Frequently in AZT than Placebo Patients

Body System Adverse Experience	Strata		N	Maximum Recorded Severity Absent	Mild	Moderate	Severe	P-Value*
Digestive	All patients	AZT	145	78 (53.8)**	49 (34)	15 (10)	3 (2)	<0.001
		PCB	137	112 (82)	14 (10)	9 (7)	2 (1)	
Nausea	AIDS	AZT	85	53 (62)	29 (34)	[illegible]	1 (1)	0.0[illegible]
		PCB	75	57 (76)	11 (15)	7 [illegible]	0 [illegible]	
	ARC	AZT	60	23 [illegible]	20 [illegible]	16 (27)	1 [illegible]	
		PCB	62	53 (85)	7 [illegible]	2 [illegible]	[illegible]	<0.001
Musculoskeletal	All patients	AZT	145	[illegible]	[illegible]	[illegible]	[illegible]	
		PCB	137	[illegible]	1 [illegible]	1 [illegible]	[illegible]	0.0[illegible]
Myalgia	AIDS	AZT	85	77 [illegible]	[illegible]	[illegible]	[illegible]	
		PCB	75	[illegible]	[illegible]	1 (1)	[illegible]	0.0[illegible]
	ARC	AZT	60	[illegible]	[illegible]	[illegible]	[illegible]	
		PCB	62	[illegible]	1 [illegible]	[illegible]	[illegible]	0.0[illegible]
Nervous	All patients	AZT	145	[illegible]	[illegible]	[illegible]	[illegible]	
		PCB	137	[illegible]	[illegible]	[illegible]	[illegible]	0.0[illegible]
Insomnia	AIDS	AZT	85	[illegible]	[illegible]	[illegible]	[illegible]	
		PCB	75	[illegible]	[illegible]	1 (1)	[illegible]	0.318
	ARC	AZT	60	[illegible]	[illegible]	[illegible]	[illegible]	
		PCB	62	[illegible]	[illegible]	[illegible]	[illegible]	0.[illegible]

*Analyzed by Cochran-Mantel-Haenszel method.

**Numbers in parentheses are percentage of total N

(95

Photosensitivity occurred more often in placebo patients than AZT patients (3% vs 0%, p=0.041).

Clinical adverse experiences which occurred in >10% of the patients were anorexia, asthenia, diarrhea, fever, headache, nausea, abdominal pain and rash. "The only one of these events which was statistically more frequent in AZT recipients is nausea, as described previously. Although the total number of headaches was not statistically different between the two treatment groups (all patients: p=0.100; AIDS: p=0.094; ARC: p=0.083), 48% of AZT recipients complaining of headache rated the maximum severity as moderate or severe, compared to 24% of the placebo .... No patient discontinued from study participation due to headache."

Three episodes of bleeding were reported, all in AZT recipients. They were painful bleeding gums in a patient with gum disease which required oral surgery, mild nose bleeding, and mild rectal bleeding. All the episodes stopped despite continued AZT treatment.

Four AZT recipients and one patient receiving placebo reported hives. All resolved despite continued administration of study drug.

c) Clinical Laboratory Data

Each patient enrolled in the trial was monitored weekly for four weeks and then biweekly until the termination of study drug for signs of possible drug-induced biochemical or hematologic toxicity. The following laboratory values were examined: hemoglobin, hematocrit, mean corpuscular volume, complete blood count with white cell differential, platelet count, erythrocyte sedimentation rate (ESR), serum creatinine, blood urea nitrogen (BUN), electrolytes, bilirubin, SGOT, alkaline phosphatase, creatinine phosphokinase, amylase, and glucose. Standard urine analyses were performed at the same intervals. In addition, blood was obtained for the determination of serum folate and Vitamin B12 levels at entry, and at 8, 16, and 24 weeks.

a) Clinical Chemistries

According to the sponsor, "AZT did not produce significant alterations in most serum chemical values monitored to determine possible drug-induced hepatic or renal dysfunction. No increases in BUN, creatinine or bilirubin to levels defining Grade 3 or 4 toxicity (i.e. >5 x upper limit of normal) occurred in either drug or placebo recipients. In addition, very few patients had increases of BUN, creatinine or bilirubin to values even twice the upper limits of normal."

One AZT patient had an increase in SGOT to a level defined as Grade 3 or 4 toxicity (>250 IU/ml) while 10 patients who were randomized to receive placebo had similar elevations (p=0.005), as displayed in Table 4.2-1 below.

NOT counted with abnormal SGOT/PT

Table 4.2-1

SGOT Values for AZT and Placebo Patients

Treatment		SGOT (IU/ml) <350 N	250-500 Grade 3 N	>500 Grade 4 N	P-Value
AZT		142	—	1	
PCO		125	4	6	.005
Diagnosis	Treatment				
AIDS	AZT	83	—	—	
	PCO	70	2	2	.034
ARC	AZT	59	—	1	
	PCO	55	2	4	.059
T4 Cell Count Stratification	Treatment				
High	AZT	51	—	1	
	PCO	44	1	2	.287
Low	AZT	91	—	—	
	PCO	81	3	4	.007

Significant differences in the number of patients with high transaminase levels were observed in the group as a whole, for AIDS patients and for patients with low T_4 count at entry. Similar results were found for levels of serum alkaline phosphatase, although the level of significance was just under p=.05 for all patients and low T_4 at entry, as seen in Table 4.2-2 below:

(97

Table 4.3.3

[illegible]

Treatment		Alkaline Phosphatase (U/L) [illegible] Toxicity N	[illegible] Grade 3 N	>[illegible] Grade 4 N	P-Value
AZT		141	2	—	
PCB		137	5	3	[illegible]
Diagnosis	Treatment				
AIDS	AZT	[illegible]	1	—	
	PCB	[illegible]	3	2	[illegible]
ARC	AZT	[illegible]	1	—	
	PCB	[illegible]	3	1	[illegible]
T4 Cell Count Stratification	Treatment				
High	AZT	[illegible]	—	—	
	PCB	[illegible]	—	—	—
Low	AZT	[illegible]	2	—	
	PCB	[illegible]	5	3	[illegible]

3

The sponsor notes that "overall, hepatic function was stable in drug-treated patients while chemical evidence of liver dysfunction increased in placebo patients. This might reflect progression or reactivation of chronic or indolent infections involving the liver, such as atypical mycobacteria, toxoplasmosis, Hepatitis B, Epstein Barr or cytomegalovirus. These findings could suggest a positive effect of AZT therapy in preventing the biochemical or clinical manifestations of occult liver disease."

crap! AZT is stated not to have an effect on these microbe.

The sponsor also states that "changes from baseline values for individual chemistries occasionally were observed in both AZT and placebo groups. These changes varied from week to week and presented no consistent trend. The actual values observed were not considered to pose clinically relevant toxicity."

b) Special Clinical Chemistries

"Statistically significant decreases of Vitamin B12 levels compared to baseline values were observed in the AZT patients over the course of the study but not in placebo recipients. These decreases ... did not render most patients Vitamin B12 deficient ....

marrow!

"Eight of the 20 AZT patients (and 0 of 8 placebo recipients) with low B12 levels (less than 200; normal range = 180-960) did manifest some laboratory changes consistent with marrow suppression .... No changes were observed in folate levels in either AZT or placebo groups."

c) Urinalyses

"No significant abnormalities were observed on either macroscopic or microscopic examination of the urine."

d) Hematologic Toxicity

According to the sponsor, "Anemia, leukopenia, and neutropenia were the major laboratory abnormalities observed in patients who received AZT ... Grade 3 toxicity was defined as a 25-50% reduction from baseline value for hemoglobin, leukocytes, granulocytes or platelets. Grade 4 toxicity was defined as a greater than 50% reduction from baseline in any of these parameters. The majority of patients who were randomized to receive AZT in this trial experienced significant toxicity according to these guidelines .... The cumulative percent of patients found to have 25% and 50% decreases from baseline are summarized in Table 4.2-3 below.

Table 4.2-3

Cumulative Percentages of Patients with Hematologic Toxicity Defined by 25-50% and Greater than 50% Decrease from Baseline Value

Treatment		N	Hemoglobin		White Cell Number		Neutrophil Count	
			Grade 3 or 4 >25% Decrease	Grade 4 >50% Decrease	Grade 3 or 4 >25% Decrease	Grade 4 >50% Decrease	Grade 3 or 4 >25% Decrease	Grade 4 >50% Decrease
			Percent	Percent	Percent	Percent	Percent	Percent
AZT		145	37.9	8.4	65.0	34.3	62.5	52.4
PCO		155	13.3	0.7	42.2	5.9	57.0	17.3
Diagnosis	Treatment							
AIDS	AZT	83	40.0	9.6	67.5	34.9	63.5	53.4
	PCO	74	12.2	0.0	40.5	0.1	50.0	10.0
ARC	AZT	60	35.7	6.7	61.7	33.3	78.3	48.3
	PCO	81	14.3	1.6	44.3	3.3	65.6	18.4
T4 Cell Count Categorization	Treatment							
High	AZT	52	23.1	7.7	57.7	13.5	80.8	30.8
	PCO	47	14.9	2.1	46.8	0.0	59.6	17.0
Low	AZT	91	45.2	8.3	69.2	45.2	83.5	64.8
	PCO	83	12.5	0.0	37.8	9.1	55.7	13.2

(99

Many patients who entered the study began the trial with evidence of compromised bone marrow function. To more completely assess the potential risks of apparently myelosuppressive therapy in such patients, an additional analysis was performed with hematologic toxicity redefined in terms of absolute values which might place each patient at risk for serious medical sequelae, such as symptomatic anemia, opportunistic infection, or bleeding. Table 4.2-4 below lists the values used to define toxicity for those revised criteria (this definition is used by ECOG, the Eastern Cooperative Oncology Group, in evaluating experimental chemotherapy).

Table 4.2-4: Revised Grading of Hematologic Toxicity

	Definition of Toxicity	
	Grade 3	Grade 4
Hemoglobin (gm/dL)	<7.5	<5.5
Neutrophil count/mm³	<750	<500
WBC/mm³	<1500	<1000

*Statistically significant differences were observed in the numbers of AZT and placebo recipients who experienced hemoglobin, white cell and neutrophil toxicity using both grading schemes (% change from baseline and absolute value).

1. Anemia

Statistically significant differences were observed in the numbers of AZT treated and placebo patients with hemoglobin decreases to values less than 7.5 mg/dl, as seen in Table 4.2-5 on the following page. *These differences were observed in the groups as a whole, in AIDS patients, and in patients entering the study with T_4 counts less than 100 ($p < 0.001$). Statistically significant differences were not observed in the numbers of ARC patients with decreased hemoglobin ($p=0.101$), nor in those patients with high T_4 cell number at entry ($p=0.031$).* The sponsor concludes, *AIDS patients carried a greater risk for development of anemia over the course of the study.*

(100)

*The numbers of patients with these hematologic laboratory abnormalities and the cumulative percent of patients overall who experienced toxicity for hemoglobin, neutrophils, and white blood cell count are listed in Tables 4.2-5 and 4.2-6 below.

Table 4.2-5

Numbers of Patients with Indicated Hemoglobin Values

		Hemoglobin (gm/dl)			
Treatment		>7.5 N	6.5-7.5 N	<6.5 N	P-Value
AZT		103	17	13	<.001
PCO		129	4	—	
Diagnosis	Treatment				
AIDS	AZT	57	11	15	<.001
	PCO	72	2	—	
ARC	AZT	51	6	3	.101
	PCO	57	2	2	
T4 Cell Count Stratification	Treatment				
High	AZT	43	3	3	.031
	PCO	43	—	1	
Low	AZT	62	14	15	<.001
	PCO	63	4	1	

at what point in time ???

Table 4.2-6

Cumulative Percentages of Patients with Low Hemoglobin

		Hemoglobin (gm/dl)		
Treatment		N	Percent with Hb <7.5	Percent with Hb <6.5
AZT		143	24.5	12.6
PCO		137	4.4	1.5
Diagnosis	Treatment			
AIDS	AZT	83	31.3	18.1
	PCO	73	2.7	0.0
ARC	AZT	60	15.0	5.0
	PCO	62	6.5	3.3
T4 Cell Count Stratification	Treatment			
High	AZT	52	11.5	5.8
	PCO	47	2.1	2.1
Low	AZT	91	31.9	16.5
	PCO	83	5.7	1.1

Table 4.2-8 below presents another analysis of ADC toxicity, i.e. the number and percentage of AZT and placebo patients with greater than 2 gram drops in hemoglobin from baseline by week of study.

Table 4.2-8
Changes in Hemoglobin Over Time
Percent of Patients with 2 gm Decrease from Baseline Values

Week	Treatment	Percent of Patients with Absolute HGB Drop >2 Gm	Number of Patients Reported	Number of Patients Excluding Withdrawal or Transfusion
1	AZT	2.2 (3)*	135	141
	P	1.5 (2)	133	137
2	AZT	5.3 (7)	131	139
	P	1.6 (2)	127	131
3	AZT	13.1 (16)	122	135
	P	2.5 (3)	121	130
4	AZT	16.4 (20)	124	134
	P	4.1 (5)	122	126
6	AZT	33.6 (41)	122	127
	P	2.5 (3)	118	122
8	AZT	27.7 (31)	112	120
	P	1.9 (2)	107	117
10	AZT	27.3 (27)	99	103
	P	6.9 (7)	101	114
12	AZT	20.9 (19)	91	103
	P	13.7 (13)	95	103
14	AZT	22.8 (19)	83	93
	P	7.5 (5)	80	102
16	AZT	15.4 (10)	65	64
	P	16.4 (12)	73	73
18	AZT	12.0 (6)	50	48
	P	13.7 (7)	51	61
20	AZT	13.5 (5)	37	34
	P	15.7 (5)	32	42
22	AZT	20.8 (5)	24	22
	P	21.9 (7)	32	30
24	AZT	0 (0)	13	10
	P	15.0 (3)	20	13

*( ) Number of Patients

were
investigator
blinded
regarding

Hgb
MCV
MHC

"At six and eight weeks on study, approximately 30% of AZT patients had hemoglobin decreases from baseline of greater than 2 grams, while only 2% of placebo patients experienced similar decreases. As time on the study progressed, AZT treated patients who experienced severe hematologic toxicity were excluded from analysis by virtue of transfusion or study termination for toxicity. Therefore, the data presented are biased toward patients who did not develop complications of drug administration .... Potential differences in hemoglobin levels due to AZT administration may thus be obscured.

"The anemia observed in patients receiving AZT was macrocytic in character. Statistically significant increases from baseline red cell mean corpuscular volume (MCV) were noted in AZT-treated patients beginning in the second week of treatment. Red cell volume increased progressively over time such that the mean change in MCV by week 22 was +17.62 cu microns (placebo recipients ± 1.00 cu microns)."

According to the sponsor, "Macrocytic anemias are characteristically associated with impaired DNA synthesis. Presumably the megaloblastic changes observed in the AZT-treated patients are associated with decreases in intracellular pools of nucleoside triphosphates similar to changes observed in experimental AZT treatment of cells in vitro. These decreases may in turn limit the ability to produce mature blood elements from rapidly dividing precursors. Folate deficiency, another common cause of macrocytic anemia, was not observed in AZT-treated patients. The prevalence of macrocytic anemia in AZT recipients as a whole was much higher than the prevalence of Vitamin B12 deficiency which therefore cannot be implicated as the major etiologic agent of anemias in these patients."

(103)

Many patients with anemia received blood transfusions over the course of the study. Table 4.2-10, below, presents the percentage of patients requiring transfusion by treatment, disease classification, and number of T_4 cells at entry.*

Time frame? Base?

Table 4.2-10

Percent of Patients with Transfusions

Patient Group	Treatment	Total Transfused Percent	Those Receiving Multiple Transfusions
All	AZT	31	21
	Placebo	11	4
AIDS	AZT	46	32
	Placebo	15	3
ARC	AZT	10	5
	Placebo	6	3
Low T4	AZT	40	25
	Placebo	16	6
High T4	AZT	15	13
	Placebo	2	0

!!

According to the sponsor, in all patient classifications except ARC, AZT recipients required significantly more transfusions than placebo recipients. The clinical outcome in transfused patients is discussed later in the sponsor's analysis.

2. Leukocytes, Neutrophils, and Lymphocytes

*Patients treated with AZT experienced decreases in the absolute number of white blood cells over the course of therapy. These data, stratified by AIDS/ARC and T_4 High/Low, are summarized in the following tables.

Table 4.2-11

[illegible]

Treatment		[illegible]			
		>[illegible] n	[illegible]-[illegible] n	<[illegible] n	p-value
[illegible]		[illegible]	[illegible]	3	<.001
[illegible]		[illegible]	9	-	
Diagnosis	Treatment				
AIDS	AZT	[illegible]	27	3	<.001
	Placebo	[illegible]	6	-	
ARC	AZT	[illegible]	9	1	.001
	Placebo	[illegible]	3	-	
[illegible]	Treatment				
High	AZT	[illegible]	4	-	.316
	Placebo	[illegible]	1	-	
Low	AZT	[illegible]	32	3	<.001
	Placebo	[illegible]	8	-	

Table 4.2-13

Cumulative Percentages of Patients with Low White Cell Numbers

Treatment		n	Percent of Patients WBC <1500	Percent of Patients WBC <1000
AZT		143	27.3	2.1
PCB		153	6.7	0.0
Diagnosis	Treatment			
AIDS	AZT	83	34.9	2.4
	PCB	74	8.1	0.0
ARC	AZT	60	16.7	1.7
	PCB	61	4.9	0.0
T4 Cell Count Stratification	Treatment			
High	AZT	32	37.5	6.3
	PCB	0	-	-
Low	AZT	51	33.3	3.9
	PCB	53	9.1	0.0

27% (AZT) vs. 7% (PCB) experienced Leukopenia

Leukopenia, defined as white blood cell count <1500, was observed in 27% of AZT recipients and 7% of placebo treated patients ($p<0.001$). Suppression of white cell number was most marked in AIDS patients, and in those patients who entered the study with less than 100 T_4 cells. The differences in numbers of patients with WBC <1500 were statistically significant for all groups except high T_4 at entry. *In most cases, leukopenia in these patients was secondary to decreases in neutrophil number. Lymphocyte numbers on the other hand were noted to increase in AZT recipients in the trial. Because of the selective nature of these decreases, changes in neutrophil number are analyzed extensively below.*

"Neutropenia was observed in a high proportion of AZT treated patients, as seen in the tables below.

Table 4.2-13

Number of Patients with Decreased Absolute Neutrophil Counts

Treatment		Neutrophil Number				P-Value
		>1000 N	750-1000 N	500-750 N	<500 N	
AZT		63	22	33	23	<.001
PBO		103	19	7	3	
Diagnosis	Treatment					
AIDS	AZT	23	14	23	15	<.001
	PBO	55	12	5	2	
ARC	AZT	37	8	7	8	.002
	PBO	51	7	2	1	
T4 Cell Count Classification	Treatment					
High	AZT	33	6	8	2	.003
	PBO	43	6		1	
Low	AZT	30	16	25	21	<.001
	PBO	63	13	7	2	

Table 4.2-14

Cumulative Percentages of Patients with Decreased Absolute Neutrophil Counts

Treatment		Neutrophil Number			
		N	≤1000 Percent	≤750 Percent	≤500 Percent
AZT		143	53.8	33.3	16.1
PBO		183	21.5	7.4	2.2
Diagnosis	Treatment				
AIDS	AZT	83	65.3	43.4	18.1
	PBO	73	25.7	9.5	2.7
ARC	AZT	60	33.3	25.0	13.3
	PBO	61	16.4	4.9	1.6
T4 Cell Count Classification	Treatment				
High	AZT	52	30.8	19.2	3.9
	PBO	49	14.3	2.1	2.1
Low	AZT	91	68.1	50.5	23.1
	PBO	63	23.8	10.2	2.3

"Thirty-nine percent of AZT treated patients and 7% of placebo recipients had neutrophil counts less than 750 at sometime during the course of the trial ($p < 0.001$). Sixteen percent of the AZT group and 2% of those patients receiving placebo had neutrophil counts less than 500." In AIDS patients, 49% of AZT recipients vs 10% of placebo recipients had neutrophil counts <750, and 18% vs 3% <500, p 0.0001. The percentage of ARC patients developing neutropenia <750 was 25% (13% <500) for AZT recipients and 5% for placebo recipients ($p < 0.001$).

Of those patients who entered the study with T_4 cell number 100/mm^3, 50% of AZT recipients and 10% of placebo recipients had decreases in neutrophil counts to less than 750/ ($p < 0.001$). For neutropenia 500/mm^3, the cumulative percentages were 23% for AZT recipients and 2% for placebo recipients. "Patients with high T_4 cells at entry were less likely to develop neutropenia during therapy. Nineteen percent of the AZT treated group and 2% of the placebo patients had neutrophil counts less than 750 ($p=0.012$). Only 4% of the AZT recipients with high T_4 cells when the trial began later developed decreases in neutrophil number to less than 500, compared to 2% of the placebo group. Neutrophil counts returned to baseline values in all cases within one to two weeks of either dose reduction or drug discontinuation."

Changes in lymphocyte number were not included in grading of toxicity for this study, but the sponsor analyzed this data "since general suppression was seen in other hematopoetic elements." According to the sponsor, "Significant increases from baseline lymphocyte numbers were seen in AZT patients at weeks two through ten ($p=0.0035$ to <0.0001), after which lymphocyte counts declined. Changes in lymphocyte numbers in placebo recipients were inconsistent."

3. Thrombocytopenia

According to the sponsor, "Decreases in platelet number were rarely seen during the course of the study. Only one patient receiving AZT and one patient receiving placebo were reported to have a platelet count less than 25,000. Twelve percent of AZT recipients (17 patients) and 31% of placebo recipients (42 patients) had decreases of 25 to 50% in platelet number from baseline. Eleven percent and 5% respectively (17 and 6 patients) in the AZT and placebo groups had greater than 50% decrease in platelet number.

"In many AZT patients platelet number increased, while values for placebo patients remained unchanged. Statistically significant increases from entry platelet number were observed in AZT recipients through week 22 ($p < 0.001$ weeks 1 to 18, $p=0.0088$ week 20 and $p=0.0010$ week 22). At week 16 the platelet count for AZT patients had increased from 134 K to 223 K while that for the placebo group increased from 150 K to 191 K. Increased platelet counts were documented in AZT patients with both AIDS and ARC as well as in patients entering the study with T_4 cells greater or less than 100 and were statistically significant in all groups."

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4. Bone Marrow Findings

According to the sponsor, "Bone marrow biopsies are often abnormal in patients with AIDS, therefore results of biopsies obtained from patients on this study must be interpreted with caution .... Bone marrow biopsy findings were reviewed in 6 patients receiving AZT on the Phase I study, nine patients receiving AZT on the Phase II study, and two patients receiving placebo on the Phase II study.

"Marrows in the two Phase II patients receiving placebo were normocellular .... Of the nine biopsied patients treated with AZT in the Phase II study, four had normocellular marrows, two had hypercellular marrows and three had hypocellular marrows. The hypercellular marrows showed changes similar to those ... in patients with AIDS except for the presence of mild megaloblastoid changes in erythroid precursors .... The other seven marrows showed prominent erythroid hypoplasia with megaloblastoid changes in erythroid precursors. Granulocyte precursors and megakaryocytes were generally preserved .... although many of the marrow abnormalities seen in patients treated with AZT can be seen in untreated patients with AIDS, the combination of marked erythroid hypoplasia with megaloblastoid changes is more prominent than would be expected from AIDS alone. It seems most appropriate to conclude that these changes may be due to impaired DNA synthesis associated with decreases in intracellular pools of nucleoside triphosphates seen with AZT treatment of lymphocytes in vitro."

5. Sponsor's Conclusions:

45% / 45%

"Overall 65 of 145 AZT recipients (45%) had evidence of marrow suppression using the modified Eastern Cooperative Oncology Group criteria discussed above. Twenty-eight patients (19%) had evidence of both hemoglobin and white cell suppression, 30 patients (21%) had isolated decreases in neutrophils and/or white blood cell counts, and 7 patients (5%) had decreases in hemoglobin only. Patients with AIDS and those who entered the study with less than 100 T_4 cells were at greatest risk for the development of AZT associated marrow suppression. In general, decreases in hemoglobin were observed prior to the development of neutropenia in those patients with both red and white cell suppression. However, decreases in cell numbers to a degree consistent with the definitions of Grade 3 and Grade 4 toxicity often were observed simultaneously. It appears that many patients whose marrow suppression consisted of neutropenia alone could be managed by dose reduction. In contrast, most patients who developed anemia in addition to neutropenia required interruption of therapy for return of hemoglobin values toward baseline."

AZT toxicity greater in people with AIDS ? T_4 < 100

3) Dose Changes and Their Relationship to Clinical and Laboratory Adverse Experiences

"Changes in the schedules of drug administration, including termination of study medication, were common in this trial. Table 4.3-1 below lists the modifications in dosing regimens reported for drug and placebo patients.

Table 4.3-1

Frequencies and Percentages for Dosing Changes

		Dosing Changes				
Treatment		No Change N (%)	Reduced Dosage N (%)	Therapy Interrupted N (%)	Drug Discontinued N (%)	P-Value
AZT		73 (53)	14 (10)	27 (21)	31 (19)	<.001
PCB		87 (94)	2 (1)	5 (4)	43 (51)	
Diagnosis	Treatment					
AIDS	AZT	34 (40)	11 (13)	16 (19)	24 (28)	< 001
	PCB	45 (47)	1 (1)	3 (4)	26 (55)	
ARC	AZT	39 (63)	3 (5)	11 (18)	7 (12)	.011
	PCB	42 (60)	1 (2)	1 (2)	17 (27)	
T4 Cell Count Stratification	Treatment					
High	AZT	30 (72)	3 (9)	7 (13)	5 (9)	.031
	PCB	34 (72)	2 (4)	1 (2)	10 (21)	
Low	AZT	35 (50)	11 (12)	20 (22)	26 (29)	<.001
	PCB	53 (59)	-	4 (4)	33 (37)	

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At the time the study was discontinued the medication history ... for each patient was reviewed and each participant was assigned to one of the following categories: 1) no change in medication, 2) continuing at a reduced dose, 3) previously interrupted therapy but now receiving drug, or 4) currently off drug .... The distribution of patients in these dose categories was then analyzed using the Cox-Mantel-Haenszel test .... Overall, the patients who received AZT during the trial had significantly more changes in dosing regimens than placebo patients ($p<0.001$). Significantly more dose modifications were observed in AIDS patients and those with low T_4 cell number at entry ($p<0.001$) .... In general, permanent discontinuation of drug because alternative medical care was needed or because the patients died was more common in placebo patients than in those receiving AZT.

When the study was terminated .... Fifty-one AZT recipients (87%) and seven placebo patients (5%) had changes in their dose schedules (including temporary discontinuation) during the treatment trial ($P<0.001$) .... The number of patients requiring dose modifications increased over time for AZT recipients .... At 4 weeks of the trial, 90% of the 137 remaining AZT patients continued full dose medication ... compared to 58% of the 130 placebo patients remaining in the trial. The percent of patients in the AZT group receiving full dose drug decreased to 52% (31 of 60 remaining patients) at 20 weeks. In addition, 33% (20 of 60) had been reduced to an every eight hour schedule and 15% (9 of 60) were temporarily off drug at that time .... Most of the dose modifications observed in the study occurred in AIDS patients with low T_4 cells ....

Table 4.3-2 on the following page lists the reasons for the initial dose reductions or discontinuations in AZT and placebo recipients.

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Table 4.3-2
First Dose Deficiency

Reason	AZT		Placebo	
Hematologic				
Decrease Hb/Hct/platelet	5**		6**	
Leukopenia/neutropenia	1*		2**	
Decrease Platelets	4*		0	
Total Hematologic	Case Discontinued 32	On Therapy 17	Case Discontinued 3	On Therapy 4
Serious Infections				
CMV retinitis/colitis	1		3	
Pneumocystis carinii	1		6	
Other pneumonia	0		2	
MAI or TB	4		2	
Toxoplasmosis	3		1	
Cryptococcus	1		0	
Total Serious Infections	Case Discontinued 0	On Therapy 10	Case Discontinued 0	On Therapy 14
Other Medical				
Nausea/Vomiting	1		0	
Indigestion	0		1	
Chemical Hepatitis	0		1	
Elevated LFT's	2		2	
Headache	1		0	
Fever of unknown origin	1		0	
Seizure	0		1	
Rash/psychiatric	1		0	
Drug overdose	2		0	
Lymphoma	0		1	
Progressive KS	0		1	
Cardiomyopathy	0		1	
Acute encephalopathy	0		1	
Pulmonary emboli	1		0	
Adrenal insufficiency	0		1	
Debilitation	0		3	
Total Other Medical	Case Discontinued 3	On Therapy 6	Case Discontinued 2	On Therapy 11
Administrative				
Noncompliance	2		2	
Protocol violation	2		1	
Voluntary withdrawal	1		7	
Total Administrative	Case Discontinued 0	On Therapy 5	Case Discontinued 0	On Therapy 10
TOTAL	78		43	

*6 patients had both anemia and leukopenia/neutropenia
**1 patient had both anemia and leukopenia/neutropenia
†1 patient had both anemia + thrombocytopenia

n=21

17 18
11
10 10/9
6
5

38 39

PL

"Patients receiving AZT were more likely to have their medication decreased or discontinued for hematologic toxicity and then resume study drug at a modified dose. AZT was most often permanently discontinued for administrative reasons .... For AZT recipients, dose modification for opportunistic infections and other medical reasons occurred early in the trial and then decreased in frequency, while dose changes for hematologic toxicity occurred later in the study. Events which led to dose reduction or drug discontinuation in the placebo group were more evenly distributed throughout the course of the study."

a) Clinical Outcome in Patients Who Experienced Hematologic Toxicity

During the course of the study 68 AZT patients (45%) and 16 placebo recipients (12%) developed evidence of marrow suppression manifested by anemia (Hgb <7.5 gm/dl), neutropenia (neutrophil count <750) or leukopenia (WBC <1500). Opportunistic infections were diagnosed in 16 AZT recipients with marrow suppression (25%) and in 8 of the 68 AZT recipients who did not experience hematologic toxicity (10%). The percent of patients with opportunistic infections in the AZT group as a whole was 17%. Therefore development of hematologic toxicity seemed to be related to an increased risk of diagnosis of opportunistic infection. The distribution of infections in both groups is indicated in Table 4.3-3 below.

Table 4.3-3

Development of Opportunistic Infections (OI) in AZT Patients

	N	Number of OI	% of Total OI's as:			
			PCP	[illegible]	CRYPT	TOXO
Patient with evidence of marrow suppression	63	16 (24.2)*	11 (68.8)**	3 (18.8)**	1 (6.2)*	1 (6.2)*
Patients with NO evidence of marrow suppression	68	8 (10.3)*	3 (37.5)**	3 (37.5)**	2 (25)*	0

*Number in parenthesis indicates percentage of patient group as a whole.
**Number in parenthesis indicates percentage of total OI for each toxicity group.

"In 7 of 16 marrow-suppressed AZT patients (44%) opportunistic infections were diagnosed within the first six weeks of therapy. These adverse events preceded the onset of hematologic toxicity. Of the 9 remaining patients, 5 developed opportunistic infections following dose reduction or discontinuation of AZT for toxicity. The interval between dose modification and documentation of infection varied from two to eight weeks. In all patients, hematologic toxicity had resolved before the diagnosis of opportunistic infection was established. In one patient, however, onset of infection was coincident with recurrent neutropenia after AZT therapy was reinstituted. For the 4 additional patients, onset of infection preceded documentation of hematologic toxicity by 4 to 6 weeks.

"Four of the eight AZT recipients who developed opportunistic infection in the absence of marrow suppression were diagnosed within the first four weeks of the trial. Two had cryptococcal disease and two atypical mycobacterial illness. Three patients developed PCP late in the course of therapy (15, 19 and 22 weeks). MAI infection was diagnosed in the last AZT recipient at 15 weeks. Two of the PCP patients had discontinued therapy 3 and 4 weeks prior to diagnosis of OI. The third had been changed to an 8 hour schedule 1 week before diagnosis of PCP. AZT was decreased to every 8 hours in the last patient during the first week of the trial and continued at that dose until diagnosis of MAI at week 15."

1. Outcome in Neutropenic Patients

"To further analyze the possible effects of AZT-associated bone marrow suppression, the records of 23 patients with grade 4 neutropenia (neutrophil count < 500) were examined to determine if this group was at particular risk for the development of opportunistic infections or other adverse outcomes .... Seven of the 23 neutropenic patients developed opportunistic infections during the course of the study (30%). This compares to a 17% OI rate in AZT recipients overall and the 25% rate of OI for AZT treated patients with any evidence of marrow suppression. Onset of infection occurred prior to the documentation of neutropenia in 4 (of the 7) patients and followed neutropenia by 1, 6, and 10 weeks in the remaining (3) patients. Five of these 7 AZT recipients who developed opportunistic infections had multiple manipulations in their dosing regimens, including several weeks when medication was discontinued.... No patient with drug-associated neutropenia developed manifestations of chronic or severe bacterial infection (with the exception of one patient with MAI disease). The development of severe neutropenia occurred in patients with low T_4 cells at entry. Four of the 23 patients with neutrophil counts less than 500 were continued in the trial without AZT dose reduction. Neutrophil counts in 2 of these patients increased on the full dose regimens."

2. Outcome in Patients Receiving Transfusion

"Forty-six patients who were treated with AZT required red blood cell transfusions during the study period. In 37 of these 46 patients the AZT dose was modified for hematologic toxicity. Thirteen of 46 transfused patients (28%) developed opportunistic infections, compared to 11 of 90 (11%) patients who did not require transfusion for anemia. Four of the thirteen infections in transfused patients were diagnosed within the first six weeks of the study. In the remaining patients, with one exception, opportunistic infections occurred at weeks 13 to 22 of the trial and followed extended periods of dose modification and interruption of therapy.

"Opportunistic infections were documented in two of nine patients who were maintained on transfusion therapy rather than decreasing AZT dose (one patient developed PCP during the first weeks of the trial and the other was transfused at the fifth week of the trial coincident with the diagnosis of cryptococcal disease) .... Leukopenia or neutropenia occurred in only 3 of the 9 patients whose hemoglobin toxicity was managed by transfusion without dose reduction. The other six patients had decreases in hemoglobin only ...."

4) Parameters Associated with the Development of AZT Toxicity

a) Laboratory Values at Entry into the Study

"Because significant bone marrow suppression was observed in AZT recipients during this trial, hemoglobin, white blood cell counts, neutrophil number, T_4 cell number, Vitamin B12 levels and folate levels at entry were examined to determine if any of these laboratory values could serve as a predictor of hematologic toxicity. T_4 cell number at entry was associated with the later development of anemia. The probability of developing hemoglobin < 7.5 gm/dl was .35 for AIDS patients with $T_4 < 100$ and .24 for ARC patients with low T_4 counts. The probabilities of similar toxicity for AIDS and ARC patients with high T_4 cells were .15 and .10 respectively.

"Several laboratory values at entry were predictive of AZT-associated neutropenia. Entry hemoglobin, neutrophil count, T_4 cell number and Vitamin B12 levels all were associated with decreases of absolute neutrophil counts to less than 750 .... Neutropenia was more prominent in those patients who entered the study with T_4 cell counts less than 100. Within this subgroup of patients with low T_4 cell counts at entry, AIDS and ARC patients had similar probabilities of low neutrophil counts.

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b) Concomitant Use of Medications Other Than AZT

"The effect of administration of acyclovir, trimethoprim/sulfamethoxazole, pyrimethamine, other sulfa containing compounds, aspirin-containing products, acetaminophen-containing drugs, and ketoconazole was examined to evaluate possible potentiation of hematologic toxicity. Only acetaminophen was associated with any potentiation of marrow suppression. Patients who took acetaminophen developed low neutrophil counts (p=.03). The association of neutropenia with acetaminophen use is presented in Table 4.4-2 below.

Probability of Developing Neutropenia
in Patients Taking Acetaminophen

Length of Recorded Use of Acetaminophen

Baseline Groups		None	2 Weeks	4 Weeks	10 Weeks
T4 < 150	ANC	.47	.53	.57	.75
	ADC	.41	.45	.50	.67
T4 > 150	ANC	.24	.29	.36	.54
	ADC	.13	.13	.20	.35

"Metabolization, i.e. AZT, is metabolized by glucuronidation, primarily in the liver .... The effect of serum levels of AZT on hematologic toxicity will be analyzed.

Antiviral drug!! !!

"Seventy of 282 patients enrolled in this trial (25%) received zidovudine (AZT) in addition to their study medication. Thirty-four were patients randomized to receive AZT ... no evidence of increased hematologic toxicity .... Only 2 of the 34 patients (6%) who received AZT in addition to AZT developed opportunistic infections over the course of the trial compared to 32 of 111 (29%) of the AZT recipients who did not receive AZT during the study."

5) Deaths (as related to safety)

"Only one death was reported in an AZT-treated patient during the course of the trial, compared to 10 deaths in placebo recipients .... Death in this (one AZT) case was related to infectious complications underlying HIV induced immune deficiency, and was not felt to be the result of drug toxicity." 1/10 2 6

6) Serum levels of AZT

"Serum samples for the determination of levels of AZT were collected on several occasions. Samples were drawn just prior to a dose and at approximately 1.5 hours after the dose. Twenty-one patients receiving AZT exhibited mean (± s.d.) predose and post dose AZT levels of 0.19 ± 0.17 and 0.80 ± 0.33 ug/ml, respectively .... There was no obvious correlation between serum AZT levels and evidence of toxicity."

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7) Central Nervous System Evaluations

"Lumbar punctures were performed on certain patients demonstrating clinical signs and symptoms of neurological disease. Cerebrospinal fluid was analyzed for content of blood cells, protein, etc. Additionally, neuropsychologic assessments were performed twice prestudy and then every eight weeks during the treatment period to measure cognitive and motor function. These analyses have not been completed at this time of this initial report. Data will be presented, when available, as an update to this report."

D. Smoser's Summary Discussion of Efficacy and Safety

"The most striking benefit of AZT administration was a remarkable decrease in mortality (< 0.001) .... The probability of 24 week survival for the AZT group was .69 compared to .33 for the placebo group. Significant statistical differences for mortality exist between the treatment groups for patients with both AIDS (P 0.001) and ARC (p=0.010).

"Patients receiving AZT also experienced significantly fewer opportunistic infections during this trial when compared to placebo recipients (p< 0.001 using Cox's regression model).... In opportunistic infections occurred in AIDS patients after receiving six weeks of AZT while the probability of developing an OI after 6 weeks was 0.23 in the placebo recipients (p=0.002)....

6 weeks. 0

6 weeks. 1

"... AZT recipients had significantly increased numbers of T helper (T_4) cells as compared to placebo patients who experienced progressive declines ... and were also much more likely to develop delayed type hypersensitivity reactions to intradermal antigenic challenge. Twenty-nine percent of patients receiving AZT had at least one positive skin test, as compared to 5% of placebo patients (p< 0.001).

"The virology data presented in this report are limited .... No elimination of infectible HIV was observed in the preliminary analysis of data. Two independent groups have analyzed HIV cultures from AZT treated patients in Miami and San Francisco and find decreased virus activity with treatment ....

"Patients receiving AZT experienced significantly improved values for performance status, body weight and clinical symptoms when compared to placebo patients.

"... the present analyses indicate that AZT altered the natural course of HIV infection. AZT either halted disease progression or rendered patients more responsive to conventional therapy for their opportunistic infections.

"Clinical adverse experience reporting was confounded by signs and symptoms associated with HIV infection. Adverse experiences which were reported substantially more frequently in the AZT group were anemia, insomnia and myalgia .... There were no changes observed in ECG, creatinine or urinalyses to suggest drug-induced renal dysfunction nor were there changes in liver function tests which might indicate drug-induced hepatotoxicity.

"The major laboratory abnormalities associated with AZT administration were hematologic .... Twenty-five percent of AZT recipients and 4% of placebo patients experienced decreases of hemoglobin to less than 7.5 gm/dl. Leukopenia (WBC <1000) was observed in 21% of the AZT group and 3% of placebo recipients. Decreases in neutrophil count to less than 750 were seen in 18% of drug and 3% of placebo patients .... Patients with AIDS and/or low T4 cell number at entry were those in whom AZT associated hematologic abnormalities were most likely to be encountered.

"The amphotericin B dose limiting changes observed in AZT patients are consistent with impairment of DNA synthesis .... Eighteen of the 32 patients whose AZT was initially discontinued for hematologic indications eventually required at least temporary discontinuation of AZT ... In an additional 17 patients AZT was initially discontinued when abnormal values were encountered .... Hemoglobin, white blood cell counts and absolute neutrophil counts returned toward baseline values while the patients were off drug. ...These observations suggest that the development of opportunistic infections in AZT patients in this trial is related to interruption of therapy as much as to drug-associated hematologic toxicity.

"The results of this placebo controlled trial clearly indicate that AZT can significantly alter the morbidity and mortality associated with ARC and AIDS. AZT produced positive clinical effects including reduced mortality, decreased incidence of opportunistic infections, maintenance of high performance scores, weight gain, decreased HIV-associated symptoms, and improved measures of immune function.

"The hematologic toxicity observed in this study should serve to caution physicians to use this drug with care. Depending upon whether hemoglobin, white blood cell count or neutrophils are used as a monitor, 40% to 80% of patients with AIDS and less than 100 T4 cells at entry developed some AZT-associated marrow suppression. Risk factors for the development of hematologic toxicity have been identified by this study and careful patient management of those with risk factors is both necessary and possible. This study suggests that AZT is an important therapeutic modality for patients with advanced HIV infection."

19/32 AZT reg. at least temporary discontinuation What if they had continued?

II. Reviewer's Analysis of Placebo-Controlled Trial

A. Demographics of Patient Population

1) Patient Population

The hundred and eighty-two patients (one a double entry) were entered over a four month period into this placebo-controlled trial of AZT at twelve centers (12-24 patients per center). One hundred and ninety (190) were AIDS patients who had recently recovered from their first episode of PCP, and 192 were "asymptomatic" patients (claimed entry criteria of > 400 or > 15 lb weight loss over the previous 3 months and/or documented oral candidiasis). All patients were required to be orphic and have a absolute T-helper cell count of less than 300/mm³ at entry. Patients were stratified separately at entry according to whether their latest T4 count was less than or greater than 100/mm³. Most patients had two screening evaluations prior to entry and a third at entry. Because all three values were not always on the same side of 100, some patients were randomized to either the high or the low T4 cell stratum at entry with only one of the three values in that category. For purposes of analysis after the trial ended, an average of all pre-entry T4 values was used as the baseline number for comparisons with changes while on therapy.

According to the sponsor, three patients did not meet all the inclusion criteria at entry, but had been eligible during the two-week pre-entry evaluation and so they were allowed to continue. These entry "violations" consisted primarily of small changes in certain laboratory criteria, according to the sponsor. Five patients had absolute T4 counts greater than 300 (up to 402), two AIDS patients (out of a total 190) were greater than 120 days from diagnosis of PCP (up to 152), eleven patients had hemoglobin < 8.5 gm/dl (as low as to 7.5 gm/dl), four had platelet counts < 75,000/mm³ (one as low as 19,000), five had SGOT > 150 I.U. (one was 530), and two did not have cytomegalovirus antibody at entry, as required. In addition, four patients violated entry criteria for other reasons; one for steroids, one for IV, one for insufficient weight loss, and another for "error." The sponsor does not state and apparently did not look into how any violations may have occurred based on inaccurate or misinterpreted items in the medical history. My inspection of the study centers indicated that some patients were entered despite disputes in the hospital records that could render them ineligible. If these apparent protocol violations were randomly distributed between the treatment groups, it should not have had a significant impact on the analyses of the major efficacy parameters, but could alter subgroups analyses to some extent.

Of the total 282 patients who were enrolled, randomization between treatment groups and among subgroups (AIDS, ARC; high/low T4) appears balanced, as shown in the sponsor's tabulation below. (Numbers in parentheses added by this reviewer show distribution of patients above and below 200 T4 cells at entry):

Diagnosis	Absolute number of T4 Cells	No. of Patients AZT	No. of Patients Placebo
AIDS	>100 (<200)	[illegible] ([illegible])	[illegible] (79)
	<100 (>200)	16 (2)	12 (5)
ARC	<100 (<200)	[illegible] ([illegible])	27 ([illegible])
	>100 (>200)	37 ([illegible])	[illegible] ([illegible])
Total		145	137

As can be seen, more than 90% of the AIDS patients enrolled had a T4 count less than 200, and over half of the ARC patients had entry T4 counts less than 200, for a total of 80% of the patients enrolled.

Of the baseline demographic variables which were analyzed to assess group comparability at entry, there was only one (days since diagnosis of PCP) in which a statistically significant difference was seen between the treatment groups, as noted by the sponsor (see page 8 of this review and table below).

[illegible] Variable	AZT (N)	Placebo (N)
[illegible]	[illegible] ([illegible])	[illegible] (137)
[illegible]	[illegible] ([illegible])	[illegible] (137)
[illegible]	[illegible] ([illegible])	[illegible] (137)
[illegible]	[illegible] ([illegible])	[illegible] (137)
[illegible]	[illegible] ([illegible])	4.7 (137)
[illegible]	77.5 ([illegible])	86.5 ([illegible])
[illegible] (between [illegible] and entry [illegible])	120.9 ([illegible])	121.3 ([illegible])
[illegible]	[illegible]	[illegible]
[illegible]	6	7

In the AZT group, the mean number of days since diagnosis of PCP was 77.5, whereas it was 86.5 in the placebo group (p=0.[illegible]). The sponsor states that this 9 day difference was not felt to be clinically relevant since it did not significantly influence mortality or development of opportunistic infection during the course of the study (according to statistical regression analyses). Since the greater the number of days since the AIDS-defining event (PCP), the closer the individual is to death, (other things being equal), the question arises as to whether this statistically significant difference at baseline in days since diagnosis of PCP reflects a slightly more advanced group of patients in the placebo group at entry, even though this parameter, by itself, did not appear to have a statistically significant effect on the major outcome variables.

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The fact that there was also a trend toward a greater mean number of symptoms at entry in the placebo group (2.3 vs. 3.3; confirm 10) and a higher mean sum of symptoms scores in the same group (3.9 vs. 4.7; confirm 10) also supports the possibility of a slightly sicker group of patients assigned to placebo at entry compared to those assigned to AZT. This could not account for the highly significant difference in mortality between the treatment groups, but could possibly influence the analysis of some of the "lesser" parameters, particularly when subgroup analyses are done. Comparability of baseline demographic variables by subgroups was not examined.

2) Patient Accountability

The sponsor states that 10[4] patients were active participants in the study when it was terminated in September. Twenty-seven (27) patients had completed the protocol, and 61 patients were withdrawn from the study prior to its termination, 10 of whom were deaths (all placebo) while receiving study medication.

Reasons for Treatment Discontinuation

	AZT	Placebo
Non-medical:		
Patient request[1]	4	11
Non-compliance	1	0
Protocol violation	2	1
Medical:		
Death of Patient (while receiving study medication)	0	10
Opportunistic Infection[2]	7	8
Progressive Kaposi's Sarcoma	0	1
Other Infections	2	2
Generalized Debilitation[3]	0	7
Potential Adverse Experiences	4	0
Allergic Reaction/Patient Request	1	0
	21	40

[1]Note: one of these patients (placebo) later died
[2]Note: four of these patients (1 AZT, 3 placebo) later died
[3]Note: five of these patients (all placebo) later died

As can be seen in the Table above (also shown on page 7 of this review), four AZT vs. 11 placebo patients requested early termination (one placebo later died); no AZT and 7 placebo patients were discontinued due to generalized debilitation (five of whom later died), and 5 AZT but no placebo recipients were discontinued for potential adverse experiences, including one allergic reaction (patient withdrew). Otherwise, reasons for early discontinuation were fairly evenly divided between the two treatment groups, including discontinuation for opportunistic infection (7 in AZT group and 8 in placebo group; of these, 1 AZT and 3 placebo patients later died). A total of 21 patients in each treatment group were discontinued for reason other than death or impending death.

The mean and median duration of participation in the study for the two treatment groups were similar (120 and 127 days for AZT, 116 and 120 days for placebo).

B. Reviewer's Analysis of Efficacy

While mortality was not specified as an efficacy parameter in the original protocol, death is the seemingly inevitable outcome of AIDS, and certainly its prevention, even temporarily, must be considered important evidence of efficacy. The other major efficacy parameter analyzed in this study was time to first opportunistic infection, the prolongation of which is also an important sign of efficacy in a disease where opportunistic infections are the most significant cause of death (as well as morbidity). Other "lesser" parameters of efficacy which were monitored during the trial and analyzed for this NDA were changes in Karnofsky performance scores, body weight, AIDS-related symptom scores, and immunologic parameters (T_4 cell count and delayed cutaneous hypersensitivity testing). Substantial effort was also put into monitoring the virologic status of patients on the study.

1) Mortality: As noted by the sponsor, (see page 10 of this review), only one AZT recipient died during the trial, compared to 19 placebo recipients ($p < 0.001$ by Cox's regression model). This is obviously a highly significant result overall. One question that comes to mind is whether this event (death) occurs predominantly in one subgroup of patients. Certainly in general, AIDS/OI patients are at higher risk for death than ARC patients, but some advanced ARC patients are clinically more ill than some AIDS/OI patients, and ARC patients can die of their HIV-infection without developing CDC-defined AIDS.

In many natural history studies, decline in the absolute number of T-helper cells in the peripheral blood has been significantly correlated with progression to AIDS. Clearly this fact was appreciated by the sponsor in the design of this study (only patients with depressed T_4 counts were eligible, and further, participants were pre-stratified and randomized on this basis.) One reason for choosing 100 as the breakpoint for randomization was a concern that the sickest patients (<100 T_4 at entry) might not respond to the drug as well as patients with higher T_4 counts.

Pre-stratification according to T_4 counts at entry presupposes analysis according to these categories at the end of the study. However, this stratification was not done by the sponsor for the major efficacy endpoints of mortality and time to first opportunistic infection in the original submission of the NDA (although it was "controlled for" in the analysis by AIDS and ARC subgroups). In a telecon with company representatives on December 11, 1986, this reviewer requested an additional analysis of mortality and OI's by T_4 strata at entry, and this additional analysis was submitted on January 12, 1987. In the original NDA submission, subgroup analysis was done by AIDS and ARC diagnosis at entry, a natural division given the history of this disease and its epidemiologic case-definition, but it is not necessarily the best medical categorization for predicting progression to further OI's or death, as

previously discussed. The sponsor's analysis of overall mortality (defined as probability of 24 week survival) and by AIDS and ARC classification at entry, can be seen in the sponsor's Table below (submitted January 12, 1987).

Table 2.1-1

Probability of 24 Week Survival

T4 Count	Treatment	Probability	P-Value
Low	AZT	0.95	<0.001
	Placebo	0.70	
AIDS*	AZT	0.95	<0.001
	Placebo	0.76	
High	AZT	1.00	0.029
	Placebo	0.91	
ARC*	AZT	1.00	0.016
	Placebo	0.81	

*from original analysis (Doc. No. THRS/CS/0045)

The difference in mortality in the AIDS group (12 placebo vs. 1 AZT) remains highly significant with a p-value of < 0.001. For ARC patients (7 deaths in placebo vs. 0 in AZT patients) the p value was 0.016, also statistically significant.

When the mortality analyses were done by T_4 count above or below 100 at entry, the difference between treatment groups for patients with $T_4 < 100$ remains highly significant, while the difference in the high T_4 group becomes less significant. If the patients are divided by T_4 count at entry greater than or less than 200, there is no significant difference between AZT and placebo recipients in the > 200 T_4 group at entry, as all but one of the deaths occurred in the low T_4 group. (Please also see statistical Review of this NDA). This analysis, of course, does not demonstrate that AZT is ineffective in prolonging survival in this group of patients with T_4 counts > 200, but reflects the following two facts: 1) that not many patients with T_4 counts > 200 were studied, and 2) the event being measured (death) did not occur but once in this group during this short trial.

As stated earlier of the 20 deaths that occurred during the placebo-controlled study, 19 occurred in placebo patients and 1 in an AZT recipient. The one AZT recipient entered with AIDS and a T_4 count less than 100, and developed a severe second episode of PCP at week 15 which was treated with pentamidine. He recovered but then developed disseminated cryptococcosis for which he refused antifungal therapy, and died 5 months after beginning the study. He remained on full doses of AZT until he developed the PCP at which time his hemoglobin had dropped to 9.2 gm//dl and he was taken off study drug for 3 weeks and restarted on 250 mg q 4 h.

The remaining 10 deaths which were all in the placebo group can be characterized as follows (see sponsor's table reproduced on page 10 of this review): 12 occurred in patients with AIDS at entry and 7 in patients with ARC at entry. Two deaths occurred within 3 weeks of enrollment; both were in ARC patients enrolled at the same center. (One, with less than 100 T_4 cells at entry, died on day 10 of "possible cryptococcosis" and the other, with 230 T_4 cells at entry, died on days 21 of biopsy-positive cerebral toxoplasmosis. Presumably, both these OI's were "incubating" at entry.) Of the remaining 5 ARC deaths, two were in patients enrolled at the same center; who both had <100 T_4 cells at entry, and both were dropped from the study in the first month ft. "generalized debilitation"; one later died (day 135) of PCP, and the other died on day 84 of MAI, (neither OI was confirmed on the Case Report Form). Of the remaining three ARC patients, two had low T_4 counts (<100) at entry; one died at day 103 of "suspected TB or CMV" and the other on day 132 of "pneumonia." The last ARC patient entered with a mean pre-entry T_4 count <200 and died on day 126 of PCP.

Of the 12 deaths in placebo patients who entered with a diagnosis of AIDS, 10 were stratified to the low T_4 (<100) group, and two to the high group. Of these two patients, both had average T_4 counts at entry of less than 200 (115 and 129), one of whom entered with a T_4 count of 15, and died on day 39 of cerebral toxoplasmosis (diagnosed 5 days after entry) and cryptococcal meningitis. The other "high T_4" (129) AIDS patient died at home of "AIDS" on day 103; no autopsy was performed.

Of the 10 deaths in patients originally in the "AIDS/low T_4" category, the mean survival after entry was 111 days (range 50-150), and the reported causes of death consisted of the following: two PCP, two "pneumonia," one toxoplasmosis, one MAI, one "suspected MAI or CMV," one CMV, one pulmonary edema (with suspected MAI), and one lymphoma.

Of the twenty deaths, sixteen were in patients originally stratified to the low T_4 at entry group. Of the remaining four, three had mean T_4 counts prior to therapy of less than 200, and the sole death in a patient with a mean T_4 at entry count of more than 200 was the ARC patient who died on day 21 of toxoplasmosis; his mean T_4 count at entry was 230.

Thus, as far as mortality is concerned, virtually all the events occurred in the patients with low T_4 counts, which is not unexpected given the accumulating evidence from natural history studies that T_4 count is the parameter best correlated with poor outcome in HIV infected patients. It is also not surprising in that the majority of patients who were enrolled in this study had low T_4 counts at entry. 182/232 were originally stratified to T_4 100, 159 of whom were "correctly" assigned to this category even if their "average" pre-entry T_4 counts had been used instead of the most recent available one, and nine more of which would have

been added who were "incorrectly" assigned to the high T_4 (>100) strata at entry, for a total of 170/502 patients (60%) who actually had a mean pre-entry T_4 count of <100. Seventy-nine percent of the patients (398/502) entered with a mean entry T_4 count <200, 88% (440/502) with a mean T_4 count <300, 90% less than 400, 93% 500, with 5 patients exceeding 500 at entry.

quote

On the Case Report Forms for the patients who died, there are only a few which report biopsy or culture proof of the clinical diagnosis reported. No actual histology, pathology or culture reports are attached. The reported causes of death are listed by the sponsor on Table 3.1-3 (reproduced on page 13 of this review).

Opportunistic Infections:

OI's were defined retrospectively according to the CDC case definition of AIDS. The sponsor performed the following types of analyses (not specified in advance) to evaluate this parameter of efficacy:

1) Probability of acquiring an OI within 24 weeks
   (a) for all patients
   (b) for AIDS patients
   (c) for ARC patients

2) Probability of acquiring an OI within 24 weeks (excluding first 6 weeks)
   (a) for all patients
   (b) for AIDS patients
   (c) for ARC patients

3) Severity of worst opportunistic infection
   (a) overall
   (b) AIDS
   (c) ARC
   (d) low T_4 (<100)
   (e) high T_4 (>100)

The probability of developing an OI was not initially analyzed by high/low Tq at entry, and analysis of severity of worst OI was not done excluding OI's occurring in first 6 weeks on study. The probability of developing an OI within 24 weeks was much more likely in the placebo group than in the AZT group. Eventually, subgroup analysis was performed by both AIDS/ARC diagnosis at entry and high/low Tq stratification (greater than or less than 100 Tq cells), and can be seen in the table below from the January 12, 1987 submission (also reproduced on page 16 of this review).

Table 2.1-3
Probability of Acquiring an OI within 24 Weeks

T4 Count	Treatment	Probability	P-Value
Low	AZT	0.39	0.022
	Placebo	0.53	
AIDS*	AZT	0.35	0.004
	Placebo	0.54	
High	AZT	0.05	0.014
	Placebo	0.29	
ARC*	AZT	0.03	0.006
	Placebo	0.30	

*from original analysis

Table 2.1-4
Probability of Acquiring an OI within 24 Weeks
(Excluding Infections Occurring in First 6 Weeks)

T4 Count	Treatment	Probability	P-Value
Low	AZT	0.31	0.005
	Placebo	0.44	
AIDS*	AZT	0.30	0.002
	Placebo	0.45	
High	AZT	0.00	0.003
	Placebo	0.23	
ARC*	AZT	0.00	0.002
	Placebo	0.25	

*from original analysis

This analysis was also done excluding OI's which occurred within the first 6 weeks of treatment, as shown in the table above.

As reported by the sponsor, of the 282 patients who enrolled in the study, 69 developed at least one OI during the study period (5 developed more than one). Infections which developed after an individual withdrew from the study were supposedly not included in the analysis. Of these 69 patients who developed OI's, 24 were randomized to AZT and 45 to placebo. Twelve of the 24 AZT recipients who developed OI's had them diagnosed in the first four weeks after enrollment, and a thirteenth was dropped from the study at 4 weeks (and was diagnosed as having toxoplasma encephalitis 3 weeks later). Of the 45 placebo patients who developed OI's, eleven did so in the first four weeks, and one additional patient developed PCP at 25 weeks, after he had completed the planned 24 week study. This leaves 11 AZT and 33 placebo patients who developed OI's during the study between 4 and 24 weeks. Of the eleven AZT patients who developed OI's, all had AIDS and a low T_4 (<100) count at entry. Nine developed PCP (6 supposedly confirmed, 3 not confirmed and two developed systemic mycobacterium avium intracellulare infection (MAI). Of the thirty-three placebo recipients who developed OI's between weeks 4 and 24, 26 had been randomized to the low T_4 (<100) stratum at entry and 7 to the high T_4 ($>100/mm^3$) stratum. Of these seven patients, 5 had an average pre-entry T_4 count less than 200, and one of the remaining two had unconfirmed "AIDS-defining" HSV at week 20. Thus, if OI's which developed in the first month after enrollment (12 AZT and 11 placebo) are considered to have been "incubating" at entry and unlikely to have been prevented by an antiretroviral agent, only 2 of the remaining 44 first OI's on study occurred in patients with T_4 counts at entry greater than $200/mm^3$.

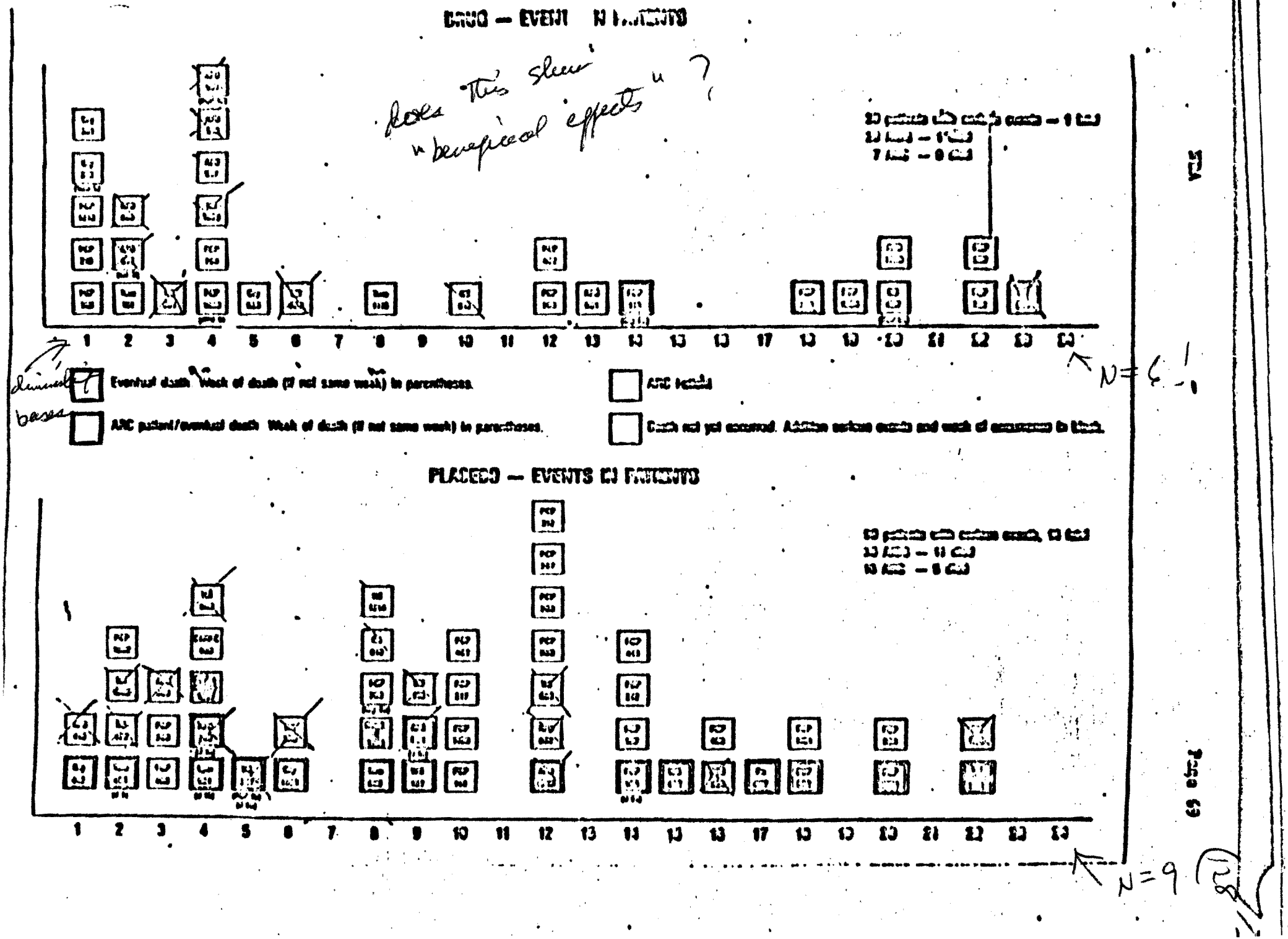
this random event appears to be the basis of FDA Logic in the LAS study.

Of the 33 placebo recipients who developed OI's, 21 were entered as ASD5 patients and nine as ARC. The OI's which developed were 20 episodes of PCP, five diagnoses of MAI, three cases of candida esophagitis (one unconfirmed by smear or culture), one cryptococcocal meningitis, one toxoplasmosis, one CMV colitis, and two ulcerative herpes simplex, neither of which were confirmed by cultures.

Of the 33 patients who died, only ten were also counted as persons with OI's, even though 17/33 deaths were reported as due to OI's. This discrepancy was (likely) due to the death-causing OI occurring after the patient was already dropped from the study, or because the OI was not "confirmed" as the cause of death.

In sum, the risk of developing an OI appears to be similar in the first four weeks of therapy, whether or not the patient is on AZT, but is significantly lower after 4 weeks in the AZT group. Since all but two of the OI's after 4 weeks occurred in patients with less than 200 T_4 cells at entry, the efficacy of AZT in reducing this risk was demonstrated within this group. For patients with T_4 counts greater than 200, this study does not demonstrate an advantage of taking AZT; there were too few patients treated for too short a period of time to make conclusions about the potential risks or benefits of the drug in patients at this stage of disease (i.e. $T_4 > 200/mm^3$).

The sponsor did not submit an analysis examining whether the risk of developing an OI over time changed with increasing duration of treatment. The risk appears similar in both groups during the initial 4 weeks. Then it falls rather sharply in the AZT group for several months, with an apparent increase again after 18 weeks (although the denominator decreases. Please see block chart on the following page prepared by the sponsor for the September 1986 meetings of the DSMB). An important question is whether the apparently increasing risk in the AZT group is paralleled by an increasing risk in the placebo group, or whether the AZT group begins to "catch up." The analysis of OI's occurring during the open label extension of this trial after September 20 may help in answereing this question. but without controls!


DRUG — EVENT
does this show "beneficial effects"?
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
N=6
Eventual death Week of death (if not same week) in parentheses.
ARC patient/eventual death Week of death (if not same week) in parentheses.
ARC relapse
Death not yet occurred. Add...
eliminate
bases
PLACEBO — EVENTS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
N=9

The sponsor did not provide this kind of block chart or do an analysis of OI's or death by time since enrollment for submission with the original NDA. This reviewer has requested this type of analysis for mortality and OI's through September 18, and also through February 13, 1987 for all patients continuing on open label AZT after September 20, and also for original placebo patients receiving AZT after September 20. (These charts have not yet been formally submitted to the NDA, but this reviewer has been given desk copies, a preliminary summary analysis of which is included in the final Summary and Conclusions section of this review.)

The potential biases in the OI data (particularly because the treatment groups may have unblinded themselves to a large extent during the first two months due to drug-induced erythrocyte macrocytosis) include the following:

1) OI's are frequently not well documented on the Case Report forms. Histological or culture confirmation of a clinical diagnosis rarely provided, and sometimes not even attempted.

2) No "standard" workup of symptoms/signs suggestive of an OI was specified in the protocol. Thus, the aggressiveness with which patients were worked up for suspected or possible infection was left to the discretion of the investigators. With randomization performed by center as well as by high/low T_4 count at entry, this lack of standardization may not have introduced significant bias, but the fact that the treatment groups unblinded themselves early could have resulted in bias in the workup of patients.

3) Infections which may have developed after an individual withdrew from the study were not included in the analyses. This would bias against drug efficacy if more OI's (and/or more severe ones) occurred in placebo recipients who withdrew compared to AZT recipients who withdrew, as was probably the case. Twenty-one AZT recipients were discontinued, one of whom later died, and 40 placebo recipients were discontinued from the study, ten because of death, leaving 30 placebo patients to potentially experience unrecorded OI's. Nine additional placebo recipients died after withdrawal (a subset of the 30), leaving twenty AZT and 21 placebo recipients who had been dropped from the protocol but were still alive at study termination on September 18 (the total duration of time off therapy for patients in the two treatment groups was not analyzed, however).

report ... by center

(130)

4)3) The sponsor's analysis of the severity of opportunistic infections in the two treatment groups was not very convincing, for several reasons:

a. Lack of objective criteria for rating severity on the Case Report Forms.

b. No severity assessment was recorded for 10 of the 69 patients who developed OI's.

c. Fatal infections were rated as most severe, and were included in the severity analysis if they occurred while the patient was still on study (all in placebo recipients). This causes the severity analysis for OI's to be unduly weighted by the mortality analysis. In any event, the difference in severity of OI's was not statistically significant although trends favored azidothymidine. (see page 17 of this review)

3) AIDS-Associated Malignancies

Less than 6% of all patients developed of Kaposi's sarcoma while on study (6 AZT and 10 placebo recipients), and there was no significant difference between the treatment groups in this regard. In addition, one placebo patient developed non-Hodgkin's lymphoma and later died of this malignancy.

4) Karnofsky Performance Status

This subjective 10 item (on a scale of 100 points) measure of ability to carry out normal activities of living (see page 18 of this review) was assessed pre-entry and monthly during scheduled clinic visits. Patients were required to have a score $\geq$ 60 ("requires occasional assistance but is able to care for most of his needs") to enter the study. The median entry score for both groups was 90, with a mean score of 89.9 for the patients assigned to AZT and 89.5 for those assigned to placebo. As noted by the sponsor, statistically significant differences in this parameter were observed between the two treatment groups overall as early as 4 weeks into therapy, and became more significant at 8 and 12 weeks (see Table 3.3-2, page 19 of this review). The differences are accounted for largely by progressive deterioration in the placebo recipients. The difference between the two treatment groups is most marked in the "low T_4" subgroup ($<$ 100 T_4 cells at entry), where statistical significance persists through 20 weeks. Statistical significance is lost after 12 weeks overall and in the AIDS subgroup, and there is no difference (or even trend) in this parameter between AZT and placebo recipients in the subgroups of "high T_4" at entry at any time, or in the ARC subgroup except at 8 weeks ($p=0.0467$). While the smaller number of evaluable patients at 16 weeks and beyond may account in part for the loss of statistical significance overall and in AIDS patients, it is apparent that patients with low T_4 cell counts at entry derive the most benefit from AZT according to this parameter.

As the sponsor notes, this type of analysis probably biases against drug efficacy because only data points from ambulatory patients reporting for their scheduled clinic visit are included. When a patient was hospitalized or was otherwise too ill to report to clinic, his data was lost for the purposes of this analysis. Since placebo patients did more poorly in terms of mortality and development of opportunistic infections, it was likely that they were more often lost to this data base than the AZT recipients.

5) Body Weight

As shown in Table 3.3-3 (page 21 of this review) AZT recipients tended to gain weight and placebo recipients lost weight, resulting in statistically significant differences between the two treatment groups beginning at 4 weeks (overall) and persisting through 20 weeks (again, the number of patients at 24 weeks reporting data was very small, which may account for the lack of significance at this point). Similar to Karnofsky performance scores, the differences between treatment groups were most dramatic in the subgroup of patients with low T_4 counts at entry, next in the AIDS subgroup, and least of all in the high T_4 at entry subgroup, where a barely significant difference ($p=0.0487$) was noted only at the 16 week visit. As with the Karnofsky scores, only ambulatory patients reporting for scheduled clinic visits contributed to this data base.

6) AIDS-Related Symptom Scores

As explained in the sponsor's analysis (pages 22-25 of this review), clinical evaluations were performed to determine the presence and severity of 10 subjective symptoms "often associated with HIV infection." These were malaise, fatigue, headache, nausea, loss of appetite, tremors, lethargy, abdominal discomfort, dyspnea, and loss of mental acuity. It is not clear why this particular list of symptoms was chosen (malaise, fatigue, and lethargy are hard to differentiate, it would seem), but it soon became apparent that there was confusion as to whether and when these symptoms, or others, should be reported as possible adverse events in addition to being recorded as part of the periodic clinical evaluation. Since the background level of some of these symptoms tends to be high in AIDS and ARC patients, but at the same time these are symptoms commonly associated with the administration of a new drug, (particularly nucleoside analogs), it is unclear how much adverse effects of the drug may have contributed to the symptom score in AZT recipients. In addition, in order to more accurately assess whether symptoms associated with AIDS-Related Complex may have been progressing as a consequence of disease or regressing as a consequence of effective treatment in both treatment groups, a combination of AIDS-related signs and symptoms should have been used instead of symptoms alone (e.g. including fever, diarrhea, night sweats, etc). The sponsor made some attempt to do this part way into the study when

??? CENSORED

a 33-item AIDS-related signs and symptoms sheet was substituted for the 10 item symptom sheet, but this data was not analyzed for the NDA since most patients were enrolled with the 10-item sheet as their only baseline data.

The sponsor's analysis of this data on change in number of symptoms from entry is displayed in Table 3.3-4 (page 23 of this review). Again, this data was collected only on ambulatory patients reporting for clinic visits. As for the analyses of Karnofsky performance score and weight changes, the differences between treatment groups which were statistically significant (overall for weeks 8,12, and 16), were most dramatic in the subgroup of patients entering with T_4 counts less than 100, and somewhat less marked in the AIDS subgroup. There were no significant differences or even trends in this parameter in the ARC or high T_4 subgroups at any time, even though ARC patients entered with higher mean symptom scores than did patients with AIDS.

Individual symptoms were not analyzed independently to see if there was a marked difference in any particular symptom over time in either the placebo or drug treated group. This type of analysis might help determine the relative contributions of underlying disease progression vs. adverse drug response for each symptom report.

Symptoms were also weighted by severity (mild, moderate, or severe) at each visit according to a subjective assessment by the physician (apparently, patients at some of the centers kept daily diaries at home, but the data from these records were not considered an "official" part of the record and they were not analyzed or submitted with the NDA). The sponsor's analysis of change in summation of symptom score from entry (Table 3.3-5, see page 24 of this review) reflects the severity score for each symptom as well as the number of symptoms (i.e. each 10-symptom sheet had a maximum severity score of 30, 3 for each item). The analysis of this data is very similar to that of change in number of symptoms alone, in that no differences were seen for ARC patients or those with high T_4 cell counts at entry, and patients with low T_4 counts at entry were the subgroup that appeared to benefit most from AZT therapy.

7) Immunology

As noted by the sponsor, T-lymphocyte subset analysis was performed twice prior to entry, at entry, and every 4 weeks on trial. Patients were originally stratified into high or low T_4 count at entry categories according to the latest available T_4 cell count, whether greater than or less than 100/mm^3, and they were then randomized to receive either AZT or placebo within these strata. While for many patients all three pre-treatment T_4 determinations fell on the same side of the 100, for some of patients they did not, and at least 16 patients were "misclassified" if the average of the pre-treatment determinations were used instead of the latest available value. In addition, according to the sponsor, five patients were enrolled whose average T_4 count was above 500/mm^3. For the purpose of analyzing changes from baseline, the mean of all pre-treatment counts were used.

As noted by the sponsor in Table 3.4-1 (see pages 23 & 27 of this review), there were highly statistically significant ($p<0.0001$) differences in T_4 count changes from baseline (through 20 weeks) between treatment groups for all patients, for AIDS patients, and for patients with low T_4 counts at entry. For ARC patients and those with high T_4 counts at entry, the differences were also statistically significant. While such statistically significant differences in T_4 counts between AZT and placebo groups across all subgroups suggests that the drug is allowing some recovery of T-helper cell numbers, several observations from this data are of concern. The first is that although absolute T-helper cell numbers increased by an average of 70 cells/mm^3 after four weeks of therapy in all AZT treated groups (overall, AIDS, ARC, high T_4 and low T_4 at entry) there was a decline in mean changes from baseline after 4 weeks overall with the value at 24 weeks (N=19) nearly back to baseline. When examined by subgroups it is apparent that AIDS patients and those with low T_4 counts at entry have the sharpest and most consistent fall in T_4 after the initial increase at 4 weeks, and that the ARC and high T_4 at baseline subgroups more or less maintain the initial increase in T_4 counts noted at 4 weeks. A second concern about this data is that the increase in T_4 numbers seen at 4 weeks is really quite modest, and does not bring the total T_4 cell count in these patients anywhere near the normal range (>800/mm^3). } !!!

AZT's "benefits" did not persist

It is unclear why the sicker patients (AIDS and low T_4) were unable to maintain the modest recovery in T_4 cell numbers seen early after initiation of therapy. One possibility is that AZT is toxic to the lymphocytes as well as to the other blood cells, thereby limiting the initial rise in T_4 counts and causing a decline again as the marrow suppressive toxicity of AZT declares itself in the other blood cell lines. If this is the case, the decline in T_4 cell number below baseline may continue as patients are treated for longer than 24 weeks. ARC and high T_4 count at entry subgroups may maintain the initial increase in T_4 numbers longer because they can tolerate the marrow toxicity of AZT better than the sicker patients, at least in the short run. The data displayed in Table 3.4-2, page 28 of this review, suggest that the decline in T_4 counts after the initial rise is largely accounted for by patients who become neutropenic, (supporting the lymphocyte toxicity theory), whereas those patients who did not experience neutropenia (<750/mm^3) maintained the initial increase in T_4 count. } !!!!!

Alternatively, the modest increase in T_4 counts in the AZT recipients at 4 weeks could be interpreted as an initial positive response to the drug, seen first as an increase in this immunologic parameter, T-helper cell number), followed by an improvement in the "lesser" clinical efficacy

Viremia, AZT's toxicities probably will persist and intensify as use of drug is continued -

parameters such as weight, symptoms, and Karnofsky performance status. The next step in the sequence of beneficial effects would be a reduction in the number of OI's in the AZT treated group, and finally a lower mortality rate. Regardless of the explanation, the important question is whether the decline towards baseline in T_4 counts in the AIDS and low T_4 at entry subgroups at 20 and 24 weeks is confirmed with data from more patients as they continue to receive AZT under the open label continuation of the trial. The next question is whether the rate of acquisition of OI's increases and finally the risk of death as treatment continues beyond 6 months.

8) Delayed Cutaneous Hypersensitivity

All but two patients were anergic at entry, as required by the eligibility criteria for the study. Skin tests to four recall antigens were performed every 8 weeks. While it seems fair to conclude that AZT recipients were more likely to develop at least one positive delayed cutaneous hypersensitivity reaction than were placebo recipients (see Table 3.4-3, page 29 of this review), the proportion of converters is well under half for those patients who had at least one skin test performed after treatment was begun (37/129=29% of AZT recipients and 11/117 = 9% of placebo recipients). The conversion rate was similar among AIDS and ARC patients receiving AZT (about 30%) but was higher among the subgroup with high T_4 counts at entry (21/49 = 43%) than among the subgroup with low T_4 counts at entry (16/80 = 20%).

The sponsor states that there appears to be no general correlation between skin test reactivation and the absolute number of circulating T_4 cells at the time the skin test became positive, in those patients who converted to positive. As can be seen in Table 3.4-5 (page 29 of this review), out of 37 positive responders among AZT recipients, 22 of the patients had a second test performed 8 weeks later. In half of these patients the repeat test remained positive and in half it returned to negative. In the 15 remaining one-time responders on AZT, a repeat skin test was not performed after the first positive response. The sponsor did not attempt to correlate positive skin test response with likelihood of developing an OI, a more important efficacy parameter. It is not at all clear what conversion from anergy to a positive delayed cutaneous hypersensitivity response means in the context of antiretroviral treatment in patients with HIV infection, or indeed in the natural history of the disease.

quote

9) Other Immunologic Tests

As the sponsor states, a number of other assays of immunologic function were performed, including circulating endogenous alpha interferon levels, in vitro blastogenic responses, and serologic testing for HIV, EBV, CMV, hepatitis B and quantitative immunoglobulins, but the data have not yet been analyzed. While clearly these analyses are not as important as the other parameters of efficacy and toxicity which were monitored, the results of these assays may help resolves the important question of whether the initial positive immunologic response in AZT patients reflected in the rise in T_4 cell counts at 4 weeks was parallled by changes in other measures of immune function, and, equally as important, whether the decline in T_4 cells seen in many "sicker" patients as time progressed was also reflected in another assay, particularly one which is not be as sensitive to T-helper cell numbers, such as changes in quantitative immunoglobulins. In addition, it would be interesting to see if changes in EBV serologies occurred independent of changes in other immune parameters in AZT recipients compared to the placebo recipients, as in vitro testing indicates that AZT has antiviral activity against Epstein Barr virus.

10) Virology

This reviewer does not have much to add to the sponsor's interpretation of the virology data which was submitted to the NDA and the explanation as to the probable reasons for its inconclusive nature (see pages 30-34 of this review). It certainly would be desirable if a definite antiretroviral effect of AZT had been demonstrated in vivo in patients receiving it under to a control group, but the sponsor's proposed explanation that the lack of a clear antiviral effect is most likely because sensitivity to "viral load" is lost when patient's cells are co-cultured for weeks in conditioned medium designed to induce latent virus and maximize viral replication, appears reasonable. Certainly this is not the only clinical trial or antiretroviral drug in which it has been difficult to interpret the virologic data obtained by reverse transcriptase assays of co-cultivated lymphocytes. What is of interest now is the apparently much greater sensitivity and reproductibility of newer antigen capture assays which may correlate with response to therapy. Paul Volberding and associates at San Francisco General Hospital recently published the results of tests on sera from patients enrolled at his center in the AZT placebo-controlled trial using Abbott's HIV-P24 antigen-enzyme-linked immunoassay. Volberding reported a decline in p24 antigen over time in the sera of patients receiving AZT compared to those on placebo. However, he did not attempt to correlate this decline specifically with either clinical outcome or immunologic parameters such as T_4 counts.

Additional analysis of serum samples from other study centers using the Abbott p24 antigen capture kit has been performed, and the results are to be submitted to the NDA. Apparently many patients' baseline serum samples were negative for HIV p24 antigen measured by this assay, limiting the significance of the results.

Clearly, as predicted from its mechanism of action, AZT does not eliminate HIV from infected patients. The problem of how best to monitor "viral load" in response to antiretroviral therapy has yet to be answered.

C. Reviewer's Analysis of Safety

1) Clinical Adverse Experiences

As discussed in the review of efficacy parameters, there was some confusion and changing instructions from the sponsor to the investigators during the course of the study regarding how and whether symptoms should be reported as possible adverse drug reactions. Apparently at first all symptoms recorded on the 10-item symptom sheet were also reported as possible adverse experiences, but later, when the 33-item signs and symptoms sheet was substituted for the ten-item sheet, the investigators were asked to make a judgment for each sign and symptom regarding the likelihood of its being a drug reaction, and only to report it on the adverse experience sheet if there was some reason to suspect a possible association (such as a clear temporal relationship to drug administration). Because so many of the AIDS-related signs and symptoms could also be adverse drug experiences, it is difficult to determine whether these events are actually disease-related or drug-related. It seems that the bias towards reporting them as one or the other (which likely varied among investigators) was altered during the course of the study from a "bias" towards "overreporting" them as possible adverse drug events at the beginning of the study, to "overreporting" them as presumptively disease-associated events later in the study. Thus it is very difficult to get a reliable evaluation of what "minor" adverse reactions the drug may have caused. The data base for analyzing possible adverse drug reactions may have changed during the course of the study as a result of the changes in symptoms forms and instructions to the investigators.

esp. since study design "unblinded"

Another confounding factor in the analysis of adverse experiences, both clinical and laboratory, was that only ambulatory patients reporting for their scheduled clinic visits reliably contributed to the data base. If patients experienced adverse reactions requiring hospitalization, or received medical attention at other locations, the details were likely to be slow in reaching the Case Report Forms for this study.

In reviewing some of the Case Report Forms, the following circumstances were noted with varying frequency:

a) Symptoms previously checked off on the 10-item symptom sheet were crossed out or otherwise changed, usually without the principal investigator's initials, and sometimes with a date of change much later than the date the form was originally filled out, without explanation as to why changes were made.

found?

b) "Transcription" of data from 10-item symptom form to the 33-item form was performed, sometimes without date or initials of who did the transcribing. Sometimes the original form was not submitted.

c) Adverse experiences were sometimes crossed out months after initially recorded, even though "possibly related to test agent" had been checked off originally by the investigator or his designee. Perhaps this was done at the same time the symptom sheets were transcribed, with the assumption that symptoms should not also be recorded as adverse events. In any case, this type of action typifies the confusion concerning the appropriate way to record symptoms and possible adverse reactions, and casts some doubt on the validity of the analyses of these parameters.

Whatever the "real" data may be, clearly patients in this study, both on AZT and placebo, reported many disease symptoms/possible adverse drug experiences. The sponsor states that, "In general, 221 of the 282 patients enrolled in the study reported at least one adverse experience for an incidence rate of 78% (122/145=84% of AZT recipients and 99/137=72% of placebo recipients). The sponsor states that in the analysis of all patients, nausea ($p < .001$), myalgia, and insomnia were the only adverse experiences reported at a significantly higher frequency in AZT recipients than in placebo recipients. The sponsor's overall assessment of the frequency of these reports is summarized in their statement "Adverse experience reporting often included events which were in reality clinical manifestations of HIV infection. This is apparent by reviewing the similar frequency of most events reported by patients receiving either AZT or placebo."

Of interest in this regard, however, is Table 4-2, Appendix A to the Medical/Statistical Report entitled "Number and Percent of Patients Reporting an Adverse Experience by Body System," in which the data are sublisted by AIDS/ARC and high/low T_4 count at entry, as can be seen on the following three pages.

clearing admission that Gould is likely

Based on all patients who began study (138
(Even though only 15 finished it.)

Appendix A: Table 4-2

Number and Percent of Patients Reporting an Adverse Experience by Body System (Excluding Definitely Not Related and Laboratory Adverse Experiences)

BODY SYSTEM	GROUP	TREATMENT N	# WITH EXPERIENCE	%
BODY	All Patients	AZT 145	83	59
		PCB 137	68	50
	AIDS	AZT 85	50	59
		PCB 75	45	60
	ARC	AZT 60	35	58
		PCB 62	23	37
	High T_4	AZT	33	62
		PCB	15	32
	Low T_4	AZT	52	57
		PCB	52	59
CARDIOVASCULAR	All Patients	AZT	1	1
		PCB	2	1
	AIDS	AZT	1	1
		PCB	1	1
	ARC	AZT	0	0
		PCB	1	2
	High T_4	AZT	0	0
		PCB	0	0
	Low T_4	AZT	1	1
		PCB	2	2
DIGESTIVE	All Patients	AZT 145	81	56
		PCB 136	57	42
	AIDS	AZT	47	55
		PCB	23	51
	ARC	AZT	34	57
		PCB	19	31
	High T_4	AZT	32	60
		PCB	13	28
	Low T_4	AZT	43	53
		PCB	44	49
HEMIC & LYMPHATIC (excluding laboratory toxicity)	All Patients	AZT	2	1
		PCB	0	0
	AIDS	AZT	1	1
		PCB	0	0
	ARC	AZT	1	2
		PCB	0	0
	High T_4	AZT	0	0
		PCB	0	0
	Low T_4	AZT	2	2
		PCB	0	0

$\chi = 1.52$

$\frac{57}{x} = \frac{42}{}$ $\chi = 1.37$

(139

Appendix A: Table 4-2 (Cont'd)

Number and Percent of Patients Reporting an Adverse Experience by Body System (Excluding Definitely Not Related and Laboratory Adverse Experiences)

BODY SYSTEM	GROUP	TREATMENT	# WITH EXPERIENCE	%
METABOLIC & NUTRITIONAL	All Patients	AZT	0	0
		PO	1	1
	AIDS	AZT	0	0
		PO	1	1
	ARC	AZT	0	0
		PO	0	0
	High T_4	AZT	0	0
		PO	0	0
	Low T_4	AZT	0	0
		PO	1	1
MUSCULOSKELETAL	All Patients	AZT	16	11
		PO	4	3
	AIDS	AZT	9	11
		PO	2	3
	ARC	AZT	7	12
		PO	2	3
	High T_4	AZT	6	11
		PO	1	2
	Low T_4	AZT	10	11
		PO	3	3
NERVOUS	All Patients	AZT	33	26
		PO	24	18
	AIDS	AZT	20	24
		PO	17	33
	ARC	AZT	18	30
		PO	7	11
	High T_4	AZT	13	25
		PO	6	13
	Low T_4	AZT	25	27
		PO	19	21
RESPIRATORY	All Patients	AZT	11	8
		PO	9	7
	AIDS	AZT	6	7
		PO	6	8
	ARC	AZT	5	8
		PO	3	5
	High T_4	AZT	5	9
		PO	2	4
	Low T_4	AZT	6	7
		PO	7	8

$z = 1.63$

Appendix A: Table 4-2 (Cont'd)

Number and Percent of Patients Reporting an Adverse Experience by Body System (Excluding Definitely Not Related and Laboratory Adverse Experiences)

BODY SYSTEM	GROUP	TREATMENT	# WITH EXPERIENCE	%
SKIN	All Patients	AZT	33	23
		PCB	33	25
	AIDS	AZT	23	23
		PCB	23	23
	ARC	AZT	8	13
		PCB	10	13
	High T_4	AZT	7	13
		PCB	8	17
	Low T_4	AZT	23	23
		PCB	27	30
SPECIAL SENSES	All Patients	AZT	11	8
		PCB	13	9
	AIDS	AZT	8	9
		PCB	8	11
	ARC	AZT	3	5
		PCB	5	8
	High T_4	AZT	2	4
		PCB	3	6
	Low T_4	AZT	9	10
		PCB	10	11
UROGENITAL	All Patients	AZT	6	4
		PCB	9	7
	AIDS	AZT	4	5
		PCB	2	3
	ARC	AZT	2	3
		PCB	7	11
	High T_4	AZT	2	4
		PCB	1	2
	Low T_4	AZT	4	4
		PCB	8	9

While for all patients the percent of AZT recipients and the percent of placebo recipients reporting adverse experiences by body system appears fairly similar (p-values are not provided), there is a much more pronounced difference in the proportions of AZT and placebo recipients reporting adverse events in the high Tq and ARC groups and a much smaller difference in the AIDS and low Tq subgroups. This is particularly true for complaints relating to the body as a whole (such as chills, fever, malaise, and headache) and for complaints related to the digestive and nervous systems, the same systems in which total number of complaints is high. By examining the "less sick" patients separately for adverse experiences, a clearer picture of what is likely to be drug related may emerge, since there are fewer "disease-associated" symptoms to confound the analysis. The high Tq at entry subgroup may be the most appropriate group to use for this sort of analysis, since there were very few deaths or opportunistic infections in this group, and therefore very few dropouts and missed clinic visits due to hospitalizations, etc. The subcategory of ARC and high Tq count at entry may be even better, but the numbers are small (AZT = 37 patients; placebo = 36 patients). This type of analysis was not provided by the sponsor.

For the three adverse events which occurred statistically more frequently in AZT patients compared to placebo patients, only nausea appears to be clinically significant (p .031; 69/145 AZT recipients reported nausea as opposed to 28/137 placebo recipients). For the other two adverse events, myalgia and insomnia, the p value was .049 for both events for all patients. Less than ten percent of patients in either treatment group reported either of these two adverse experiences at all. On the other hand, a number of other adverse events (anorexia, asthenia, diarrhea, fever, headache, nausea, abdominal pain, and rash) were reported in over 10% of patients overall, but were not statistically more frequent in the AZT group than the placebo group. Headache is an example of an adverse event which occurred more often, and was reported as more severe in more AZT recipients than placebo, but statistical analysis did not demonstrate a significant difference between treatment groups. It seems likely that AZT "exacerbated" the likelihood and severity of headache, particularly since patients were otherwise "doing better" on AZT.

The three episodes of bleeding which were reported as adverse drug experiences were mild, transient, and do not appear to be drug-related.

Several patients developed hives (4 AZT and 1 placebo). All patients continued on their assigned treatment and the hives resolved.

2) Clinical Laboratory Data

a) Clinical Chemistries

This reviewer concurs with the sponsor's conclusion that AZT does not appear to cause renal toxicity based on their analysis of serial evaluations of BUN, serum creatinine, and urinalyses.

Analyses of serial serum bilirubin, SGOT, and alkaline phosphatase values showed no evidence of clinically significant hepatotoxicity. In fact, there were statistically significant differences in the number of patients with elevated SGOT and alkaline phosphatase values in the placebo group compared to the AZT group (SGOT: 1 AZT vs 10 placebo, p = .006; alkaline phosphatase: 2 AZT vs 8 placebo, p = .047). The statistically significant differences in changes from baseline of these two parameters comparing the AZT cohort to the placebo cohort were due to small decreases or no changes in the AZT group compared with increases in the placebo patients beginning at 8 weeks. As noted by the sponsor, the reason for these differences is unknown but may reflect ongoing subchronic hepatic infections in the placebo patients which improved in patients on AZT. Of note is that by week 12, there were statistically significant differences in the change from baseline values for serum bilirubin in the AZT cohort (p=.0010 at 12 weeks, p=.003 at 16 weeks and p=.0045 at 20 weeks). The very modest (0.1 mg/dl) but persistent increase in serum bilirubin in the AZT group occurred predominantly in the AAS and high T_4 subgroups and although not clinically significant, may possibly represent a very mild AZT induced hepatic dysfunction which is masked in the sicker AIDS and low T_4 patients by underlying subchronic hepatic infection. It is unlikely to be a result of low grade red blood cell hemolysis since AZT does not appear to cause a hemolytic anemia, but may be a result of the glucuronidation of AZT in the liver. Creatinine phosphokinase (CPK) is another chemistry parameter which rose slightly in the AZT cohort compared to the placebo cohort. The difference became statistically significant at week 8 (p=.0259) and persisted through week 16. Again the average increase of between 10 and 20 units is not clinically significant but may reflect subtle toxicity to muscles.

of course, poppers cause hemolytic anemia

b) Special Clinical Chemistries

Special clinical chemistries (Vitamin B12 and folate levels) were obtained because it was known from the Phase I trial that AZT induces a megaloblastic anemia. The sponsor states that (highly) statistically significant decreases in Vitamin B12 levels compared to baseline values were observed in the AZT patients over the course of the study but not in placebo patients; however, most patients did not become B12 deficient. Twenty-eight patients (20 AZT, 8 placebo) had at least one Vitamin B12 level less than 200 (normal range 100 to 960). I agree with the sponsor that no significant changes were observed in folate levels that appear drug related.

c) Urinalyses

This reviewer agrees with the sponsor that there was no evidence of drug related abnormalities in the urinalyses.

d) Hematologic Toxicity

This reviewer agrees with the sponsor that anemia, leukopenia, and neutropenia were the major laboratory abnormalities observed in patients who received AZT. Table 4.2-3, reproduced on page 39 of this review, shows that over a third of AZT recipients experienced a greater than 50% decline in total white blood cell counts (compared to less than 8% of placebo recipients) and over half of AZT recipients experienced a greater than 50% decrease in neutrophil count (compared with less than 20% of placebo recipients). The differences were most striking in the subgroup with low T_4 cell count at entry and least striking in those with high T_4 count at entry. For hemoglobin toxicity, nearly 40% of AZT recipients compared to less than 15% of placebo recipients had a greater than 25% decline in hemoglobin. Many fewer patients in either treatment group had a > 50% decline in hemoglobin values, presumably because they were transfused before dropping that far. Similar results were obtained using criteria (see Table 4.2-4, page 40 of this review) modified from those used by the Eastern Cooperative Oncology Group to grade hematologic toxicity in patients with underlying malignancies who receive cytotoxic chemotherapy (see Tables 4.2-5, 4.2-6 page 41 of this review).

1. Anemia

As can be seen from Table 4.2-5, the difference in the number of patients with drops in hemoglobin to 7.5 gm/dl or below in the two treatment groups was highly significant ($p < .001$) for all patients, AIDS patients, and those who entered with T_4 counts less than $100/mm^3$. Strong trends in the same direction were seen in the ARC and high T_4 at entry subgroups as well.

Table 4.2-3 (page 42 of this review) displays changes in hemoglobin over time as the percent of patients in each treatment group with at least a two gram decrease from baseline values. According to this table, the maximum percentage of AZT patients (and maximum difference between AZT and placebo groups) who met this toxicity criterion occurred after 6 weeks of therapy but this degree of anemia was already apparent in >10% of AZT recipients as early as 3 weeks of therapy (compared to 2.5% of placebo recipients). It must be understood, however (as the sponsor points out), that as time on the study progressed, patients who experienced severe drops in hemoglobin (primarily AZT recipients) were excluded from analysis by virtue of transfusion or study termination for toxicity. Thus, the remainder of the table (after transfusions began) is misleading. It would be more meaningful if a "last observation carried forward" analysis was done for patients prior to transfusion or termination for hematologic toxicity.

As noted by the sponsor, the anemia in patients receiving AZT was macrocytic in character with highly statistically significant increases in mean corpuscular volume beginning in the second week of treatment, and rising progressively over time. I have no reason to disagree with the sponsor's explanation of the likely cause of the AZT-associated macrocytic anemia (i.e. decreases in intracellular pools of nucleoside triphosphates resulting in impaired DNA synthesis), as related on page 35 of this review.

Table 4.2-10 (page 44 of this review) displays the percent of patients who received blood transfusions (any and multiple) for all patients and by subgroups. For AZT recipients, AIDS patients were most likely to have been transfused and ARC patients least likely (46% and 10% respectively). For placebo recipients, patients with 100 T_4 cells at entry were most likely to have been transfused (10%) and patients with 100 T_4 cells at entry least likely (2%). Fewer ARC patients on AZT received multiple transfusions than did high T_4 patients despite the fact that ARC patients as a whole experienced more hematologic toxicity than did the cohort who entered with high T_4 values (there is an overlap between these groups, of course, with 60% of ARC patients also falling in the high T_4 at entry subgroup). Perhaps the investigators, who were presumably more aware of a patient's AIDS/ARC status than of his high/low T_4 status at baseline, were more apt to transfuse an AIDS patients than an ARC patient for the same degree of anemia, because AIDS patients are generally as sicker and perhaps less able to tolerate a comparable drop in hemoglobin.

2. Leukopenia, Neutropenia, and Lymphopenia

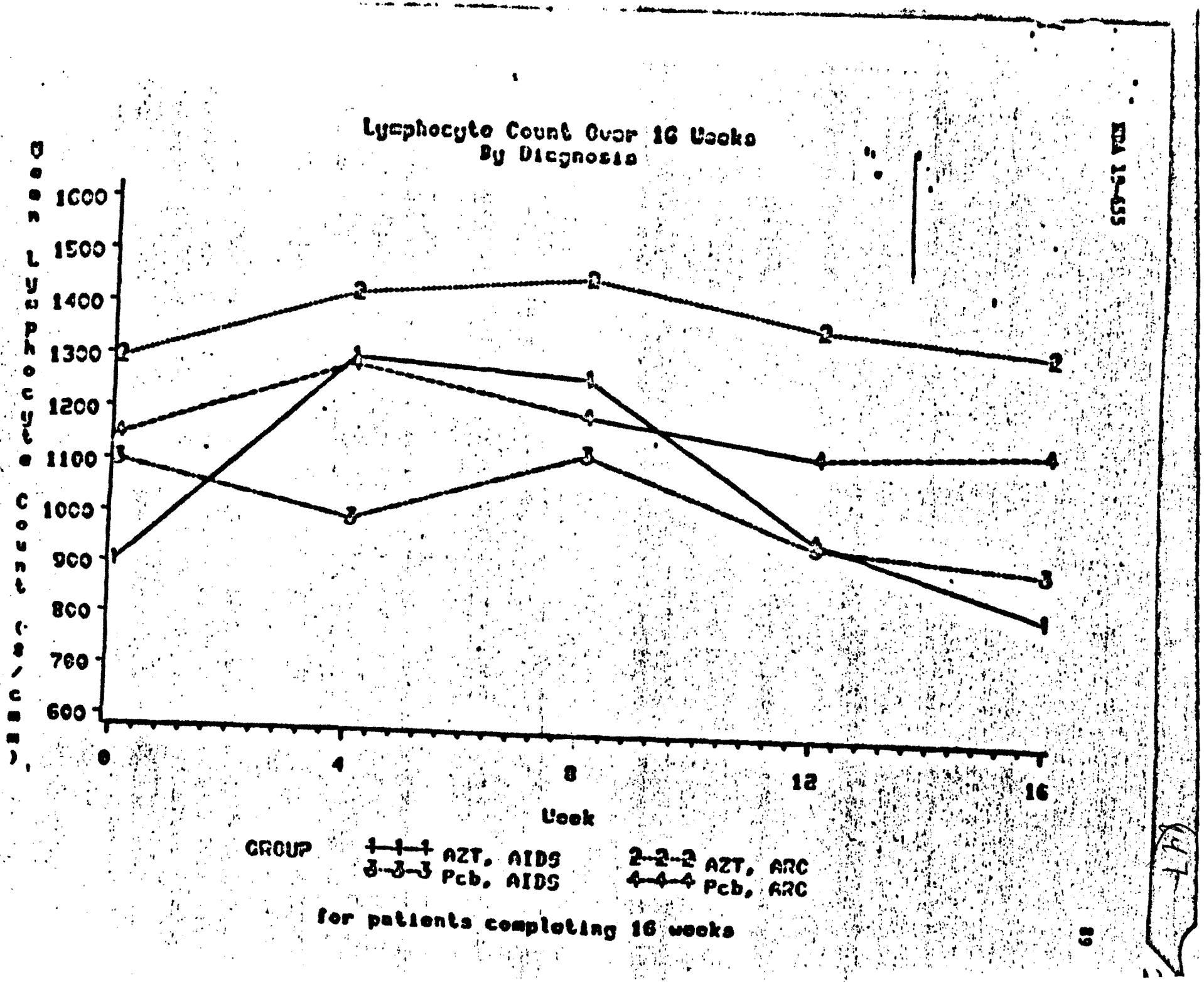
Tables 4.2-11 and 4.2-12 (pages 44 & 45 of this review) summarize the declines in white blood cell numbers in patients over the course of the study by treatment and subgroups. Overall, there was a highly statistically significant difference ($p < .001$) in white blood count decline between AZT and placebo recipients for all patients, patients with AIDS, and for patients who entered with T_4 counts 100/mm^3. The difference was also statistically significant ($p = .012$) in the ARC subgroup, but not in the high T_4 at entry subgroup ($p = .214$)

In most cases leukopenia was secondary to decreases in neutrophil number, which were observed in a high proportion of AZT treated patients. These data are summarized in Tables 4.2-13 and 4.2-14 (page 43 of this review). P-values for the differences between treatment groups for this parameter (neutropenia) are similar to those noted earlier for leukopenia, except that they are of greater statistical significance in the AZT subgroup ($p=.002$) and also reach statistical significance in the high Tq at entry subgroup ($p=.040$). The early rise in lymphocyte numbers in AZT recipients (see below) obscures this difference when total white counts are analyzed. As can be seen in Table 4.2-14, almost a quarter (24%) of patients with low Tq counts at entry who received AZT developed an absolute neutrophil count less than 500 at sometime during the trial compared to 2% of placebo recipients. For the high Tq at entry subgroup, less than 4% of both treatment groups experienced neutropenia to this degree (AIDS and ARC subgroups fell inbetween). Thus, Tq count at the beginning of treatment is a better predictor of subsequent dose-limiting neutropenia than is clinical classification of AIDS vs ARC.

The sponsor states that "neutrophil counts returned to baseline values in all cases within one to two weeks of either dose reduction or drug discontinuation," but does not refer the reviewer to a data tabulation from which this statement can be confirmed.

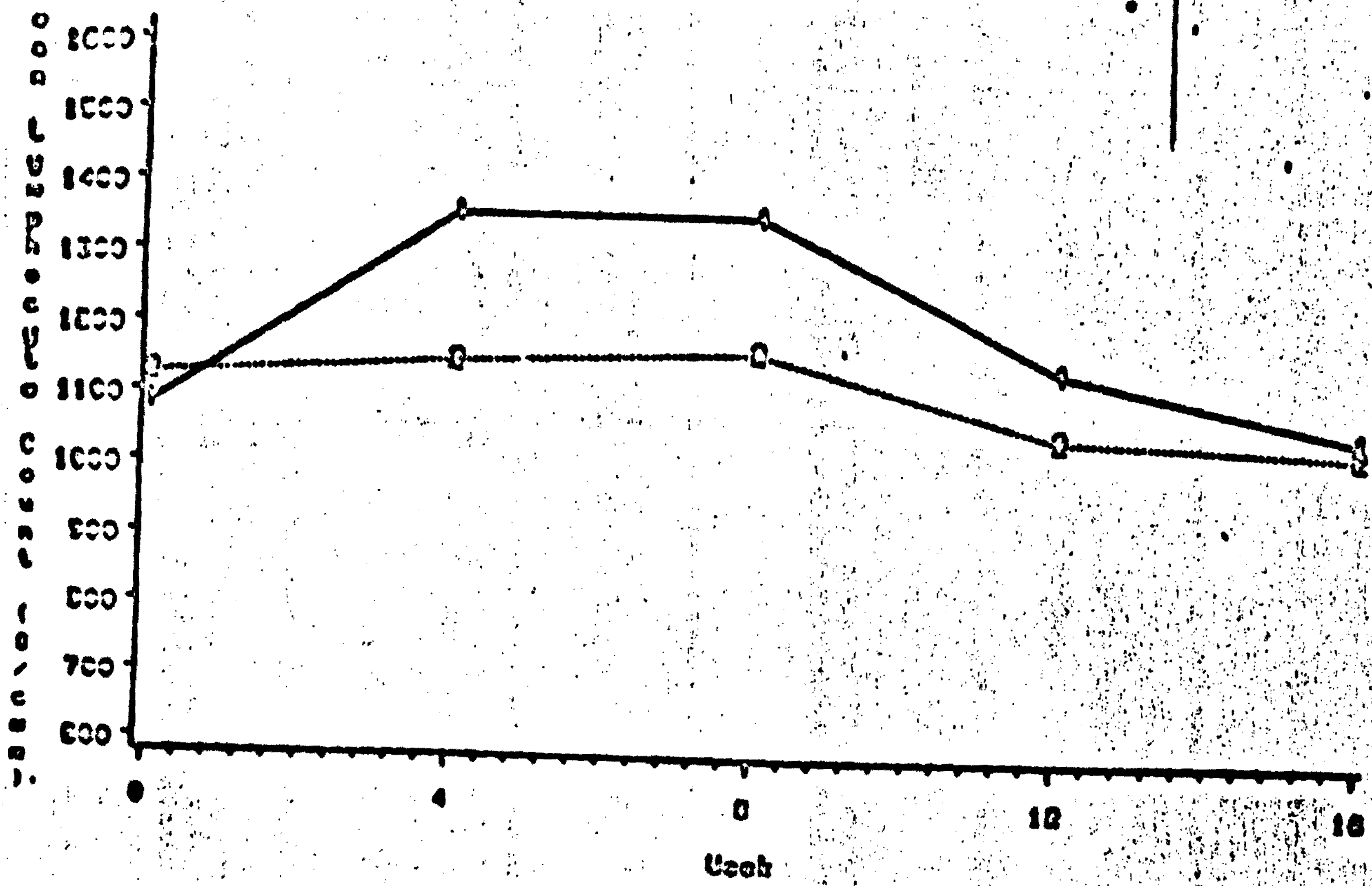
The sponsor included in their analysis a table displaying the percentage of patients with low neutrophil counts by time on study (not included in this review). It indicates that the percentage of AZT patients with neutrophil counts 1000 was greatest at 10 weeks (30% of AZT recipients compared to 7.6% of placebo recipients). Beyond that point the number of patients providing data declines (although N for each week is not provided), and many patients with significant neutropenia had dosage reductions and/or temporary discontinuations because of neutropenia, apparently followed by at least a partial recovery.

As the sponsor notes, changes in lymphocyte number were not included in the grading of toxicity for this study; however, changes in subsets of the total lymphocyte number (i.e. T-helper cell count) were followed and analyzed as a parameter of efficacy. Highly statistically significant ($p=.003$ to $<.001$) increases in total lymphocyte numbers were seen in AZT recipients overall at weeks two through ten with inconsistent changes in the placebo group. A significant ($p<.03$) increase was seen in the AZT and high T_4 count subgroups only at week 10. Thus, this early rise in lymphocyte count was almost entirely accounted for by the sicker patients (AIDS and low T_4 at entry); however, after 10 weeks even total lymphocyte number declined to below baseline levels, which reached statistical significance (for being less than baseline values) by weeks 22 and 24, despite the few numbers of patients on study for that long. The three figures prepared by the sponsor and reproduced on the following pages graphically display these differences in lymphocyte counts, but only through week 16.


Lymphocyte Count Over 16 Weeks
By Diagnosis
Mean Lymphocyte Count (cells/cmm)
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
0
4
8
12
16
Week
GROUP
1-1-1 AZT, AIDS
3-3-3 Pcb, AIDS
2-2-2 AZT, ARC
4-4-4 Pcb, ARC
for patients completing 16 weeks

NDA 19-655

Lymphocyte Count Over 16 Weeks
All Patients



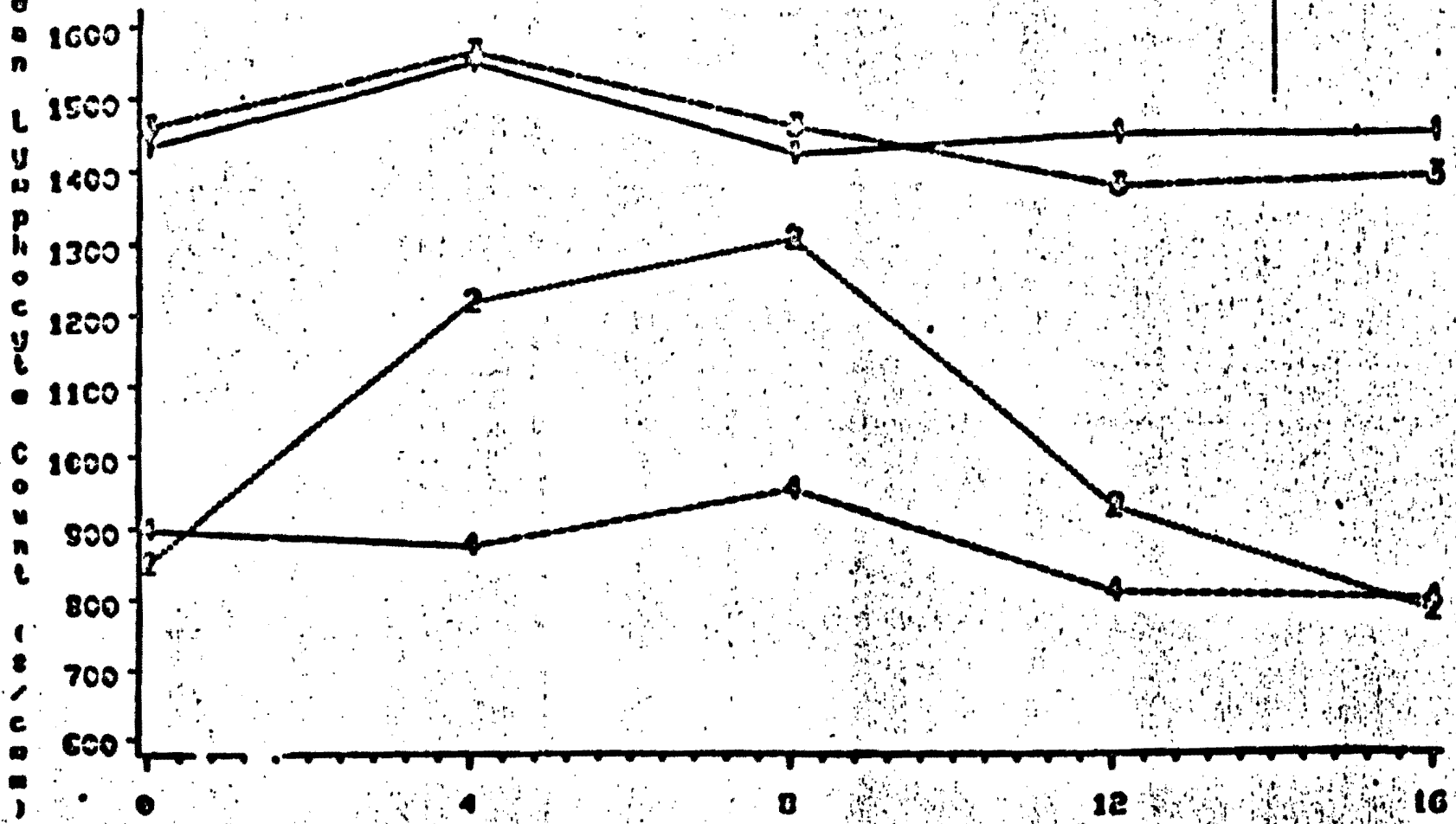
for patients completing 16 weeks

Basis???

148

8

Lymphocyte Count Over 16 Weeks
By T4 Cell Count Stratification



for patients completing 16 weeks

The comparable absolute T-helper cell numbers parallel the total lymphocyte numbers initially, but after 10 weeks, when total lymphocyte numbers are falling back to baseline in the AZT group, mean T_4 counts remain steady (or decline very slightly) for all patients. (see Figure 3.4-1 prepared by the sponsor on the following pages).

As can be seen, for subgroup analysis by AIDS/ARC diagnosis, the sharp rise and fall in total lymphocyte count in AIDS patients is paralleled, (although somewhat blunted) in the T_4 counts.

For subgroup analysis by T_4 cell count stratification at entry, there was no difference in total lymphocyte count over time between AZT and placebo recipients in the high T_4 at entry subgroup, but a sharp difference between AZT and placebo recipients in the low T_4 at entry subgroup, with a sharp rise peaking at 8 weeks followed by an equally sharp fall back to baseline by 16 weeks in AZT recipients, with essentially no change in the comparable placebo recipients (refer back to page 85).

For the analysis of changes in absolute T_4 count by T_4 stratification at entry, however a statistically significant increase in T_4 numbers is seen in both the high and low T_4 at entry subgroups by 4 weeks, followed by a gradual decline toward baseline in the low T_4 subgroup, and a sustained modest (but not rising) increase in the high T_4 count at entry subgroup.

Appendix A: Figure 3.4-1

(152

93 - 99 not supplied by FDA

FIGURE 3

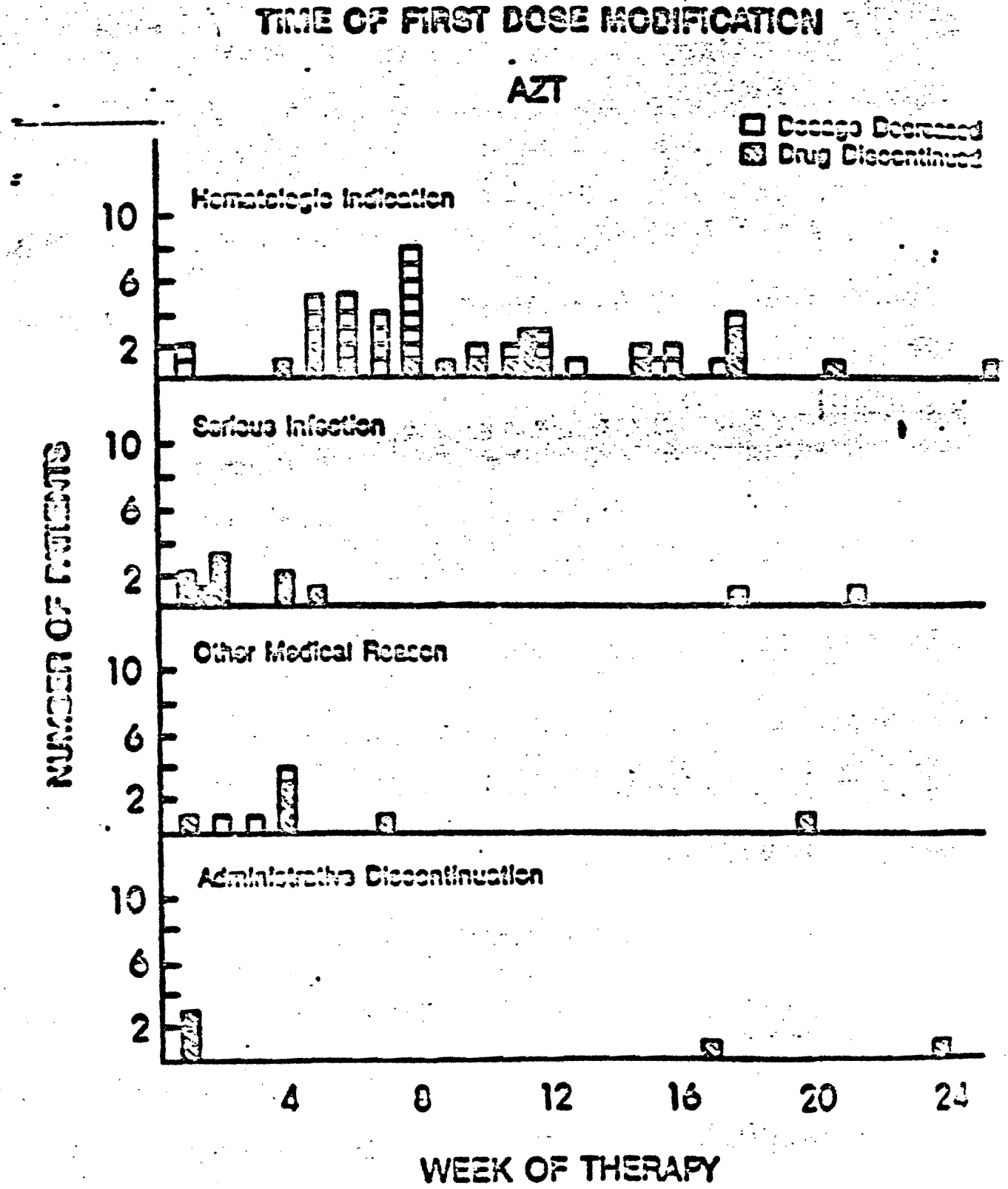
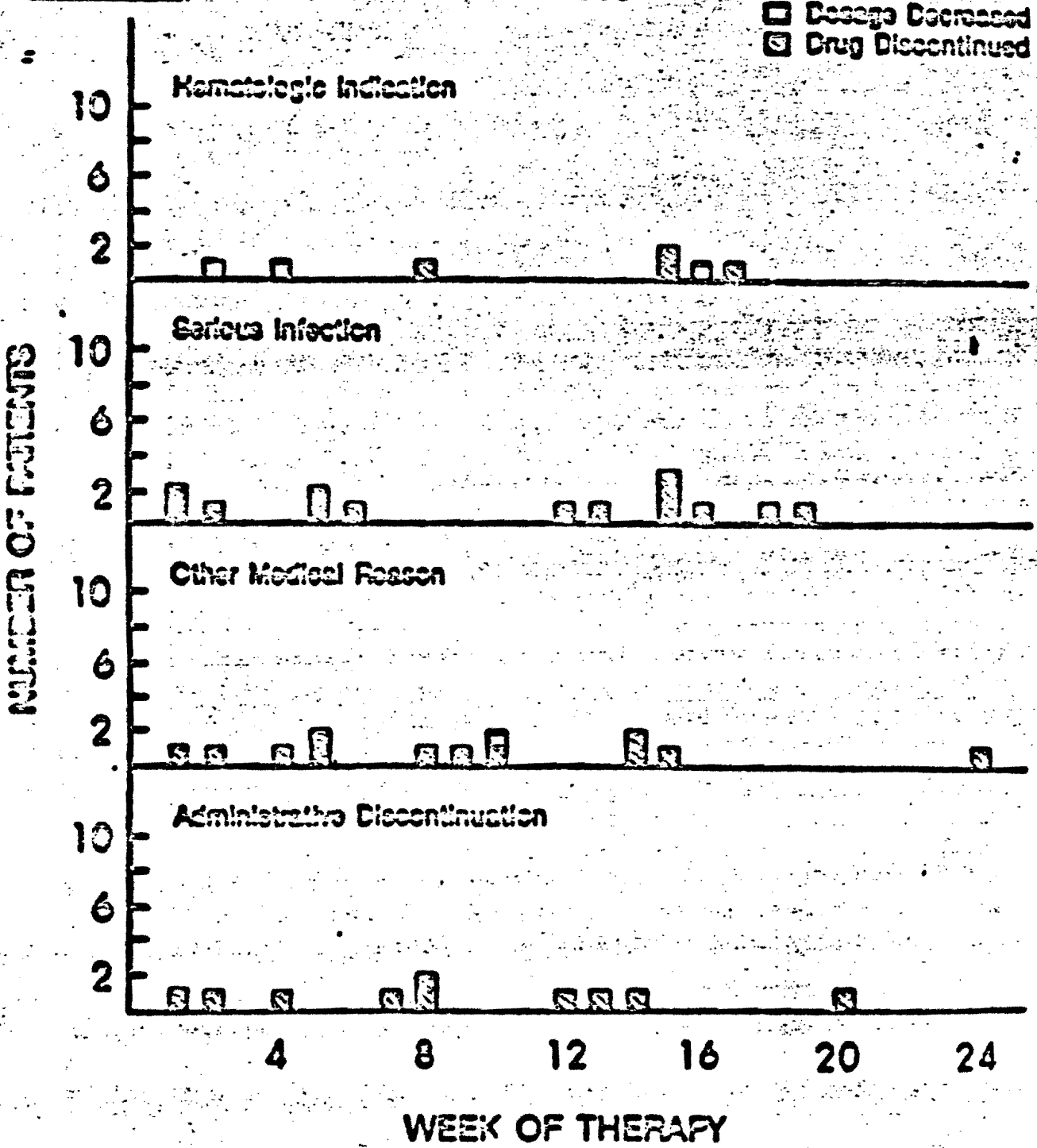

TIME OF FIRST DOSE MODIFICATION
AZT
Dosage Decreased
Drug Discontinued
Hematologic Indication
Serious Infection
Other Medical Reason
Administrative Discontinuation
NUMBER OF PATIENTS
10
6
2
4
8
12
16
20
24
WEEK OF THERAPY

FIGURE 6

TIME OF FIRST DOSE MODIFICATION

Placebo



a) Clinical Outcome in Patients Who Experienced Hematologic Toxicity

The sponsor states (see page 52 of this review) that opportunistic infections were diagnosed in 16 out of 65 (25%) of AZT recipients who developed evidence of grade III (ECOG classification) bone marrow suppression during the course of the study, and in only 8 of 80 (10%) AZT recipients who did not experience hematologic toxicity. Their conclusion that "the development of hematologic toxicity seemed to be related to an increased risk of opportunistic infection" appears true on the surface, but does not address the more meaningful question of whether or not one condition tended to predict the other. The sponsor tried to address this question but the numbers are to small to draw any conclusions about cause and effect.

The number of OIs in the AZT group after 6 weeks of therapy was small (13 patients), 9 occurring in patients with marrow suppression (4 before, 5 after dose modifications), and 4 in patients without evidence of marrow suppression.

The sponsor examined clinical outcome in patients who developed grade 4 neutropenia ($< 500/mm^3$; see page 46 of this review). There does not appear to be a particular risk of developing an OI in this group of patients (7/23 = 30%) compared to all patients with evidence of marrow suppression (16/65 = 25%), but it is higher than AZT patients overall (24/145=17%). Reliable conclusions cannot be drawn from this type of analysis since the numbers are small and not all patients in the denominator are at equal risk for developing the outcome (OI) because they were in the study for varying periods of time.

The majority (70%) of patients who received red blood cell transfusions (37/47 patients) also had dose modifications for hematologic toxicity (see page 46 of this review). Thirteen of the 47 (28%) transfused patients developed OIs (4 within the first six weeks of the study, and in the remaining 8 at weeks 18 to 22 following extended periods of dose modification and interruption of therapy) compared to 11 of 99 (11%) of patients who did not receive transfusion.

Of the nine patients who were maintained on the same dose of AZT while receiving transfusions for anemia, only two developed OI's, both within the first 6 weeks of therapy. Only three of these 9 patients developed leukopenia and/or neutropenia, according to the sponsor (one of whom developed PCP during the first week of the trial).

The "dose modification in relation to risk of developing OI" data discussed above suggests that patients who had dose modifications for hematologic toxicity had more OI's than patients who were maintained on full dose of AZT. What is not clear is whether the association of increased risk of OI's and increased hematologic

toxicity are related to each other or are independently a result of a third factor, such as severity of underlying disease. The data on patients with significant anemia who were transfused but maintained on full doses of AZT suggests that red cell toxicity alone is a result of AZT and if full doses of AZT are continued, efficacy in terms of decreased OIs can be maintained. This hypothesis that maintaining full dosage of AZT and transfuse for anemia rather than modify the dose of AZT should be tested in a comparative trial. For patients who developed white blood cell toxicity (primarily neutropenia), the management options are more limited, since other data strongly suggest that granulocyte counts less than 500 put the patient at significant risk of serious bacterial infections. For these patients, dose modification would appear mandatory (although at least two patients experienced recovery of granulocyte numbers with no change in dose of AZT). The hypothesis to be tested is whether dose reduction or temporary discontinuation is the better strategy in terms of maintaining efficacy. This thesis should also be subjected to testing in a comparative trial.

4) Parameters Associated with the Development of AZT Toxicity

a) Laboratory Values at Entry into the Study

As related on page 46 of this review, the sponsor examined a number of laboratory values at entry (hemoglobin, white blood cell counts, neutrophil number, T_4 cell number, Vitamin B12 levels and folate levels) to determine if any could serve as a predictor of hematologic toxicity in those patients who received AZT. The sponsor states that T_4 cell number at entry was associated with later development of anemia (Hgb < 7.5 gm/dl; see page 46 of this review). Several laboratory values at entry (hemoglobin, neutrophil count, T_4 cell count and Vitamin B12 level) were predictive of AZT-associated neutropenia ($< 750/mm^3$).

The sponsor then went on to generate tables "predicting" the probability of developing neutrophil toxicity depending on the patient's entry laboratory values. These are displayed on the following page.

Table [illegible]

Probability of Grade 3 or 4 Neutropenia in Patients Receiving AZT
Effect of Entry Hemoglobin and Neutrophil Count

AIDS PATIENTS

Entry T4 Cells > 100

Neutrophils (mm3)	Hemoglobin (gm/dl)		
	13.5	11.5	9.5
2000	.09*	.13	.27
1500	.13	.23	.33
1000	.18	.33	.43

Entry T4 Cells < 100

Neutrophils (mm3)	Hemoglobin (gm/dl)		
	13.5	11.5	9.5
2000	.25*	.43	.64
1500	.42	.53	.73
1000	.51	.67	[illegible]

ARC PATIENTS

Entry T4 Cells > 100

Neutrophils (mm3)	Hemoglobin (gm/dl)		
	13.5	11.5	9.5
2000	.13*	.22	.33
1500	.18	.33	.43
1000	.21	.33	.53

Entry T4 Cells < 100

Neutrophils (mm3)	Hemoglobin (gm/dl)		
	13.5	11.5	9.5
2000	.42*	.53	.73
1500	.52	.67	[illegible]
1000	.61	.76	.63

*Probability of developing Grade 3 or 4 Neutropenia

7-0135

(158

Table [illegible]

Probability of Grade 3 or 4 Neutropenia in Patients Receiving AZT
Effect of Entry Hemoglobin and Neutrophil Count

AIDS PATIENTS

Entry T4 Cells > 100

Neutrophils [illegible]	Hemoglobin [illegible]		
	13.5	11.5	[illegible]
[illegible]	.07*	.13	[illegible]
[illegible]	.13	[illegible]	[illegible]
[illegible]	.13	[illegible]	[illegible]

Entry T4 Cells < 100

Neutrophils [illegible]	Hemoglobin [illegible]		
	12.5	11.5	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	.51	[illegible]	[illegible]

ARC PATIENTS

Entry T4 Cells > 100

Neutrophils [illegible]	Hemoglobin [illegible]		
	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]

Entry T4 Cells < 100

Neutrophils [illegible]	Hemoglobin [illegible]		
	[illegible]	11.5	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	.61	[illegible]	[illegible]

*Probability of developing Grade 3 or 4 Neutropenia

These predicted values all assume an entry Vitamin B12 level of 400 (average for the study). Apparently they have not been tested against the values actually recorded from the patients treated with AZT. (Please see statistical review of this NDA). The models also do not state a duration of drug exposure to which the model should apply. The data from the patients on which it was based also were on the drug for varying durations (2 1/2 - 6 1/2 months.) Entry T_4 count was determined to be a strong predictor of neutropenia, with AIDS and ARC patients behaving similarly within the T_4 strata. Low T_4 counts at entry carried a much higher probability of developing neutropenia than high (>100) T_4 cells at entry.

b) Concomitant Use of Medications Other Than AZT

The issue of concomitant medications was considered by the sponsor and investigators in a meeting prior to initiation of this study, and it was agreed that as much as possible, no other medications should be given because it would cloud the analysis of the safety and efficacy of the test agent, AZT, and was also potentially unsafe for the patient, as drug interactions with AZT were essentially unstudied. The issue of chronic prophylaxis against PCP with low dose trimethoprim/sulfamethoxazole (TMP/SMX), and against herpes simplex infection with oral acyclovir, were specifically addressed, and the consensus of the investigators and the sponsor, written into the protocol, was to prohibit chronic usage of these agents. The following medications were specifically permitted, if needed: Septra DS mg/kg/day q 6 h x 21 days for Pneumocystis carinii pneumonia, clotrimazole troches for localized candidiasis, Kaolin-pectin products for diarrhea (Lomotil if severe), flurazepam 15-30 mg for sleep, and Zovirax 200 mg 5 x/day x 5 days for recurrent genital herpes. It was noted in the protocol that aspirin or acetaminophen may alter the metabolites of AZT and should not be used chronically. It was further specifically stated in the protocol that patients would be removed from the study if they developed an illness which required an experimental agent, drugs causing neutropenia or significant risk of nephrotoxicity, or if treatment required rifampin or one of its derivatives. Any regimen or drug not specifically prescribed or proscribed in the protocol was to require prior approval of the sponsor.

In fact, the majority of patients took other medications for varying periods of time, some chronically, while they continued to take AZT or placebo. The sponsor chose to tabulate and analyze the concomitant use of the following drugs for the possibility of increasing hematologic toxicity: acyclovir, TMP/SMX, pyrimethamine, other sulfa containing compounds, aspirin-containing products, and ketoconazole. According to the sponsor, only acetaminophen was associated with any potentiation of marrow suppression (low neutrophil counts, p=.03).

The sponsor presents a model (page 93 of this review) which predicts that the probability of developing neutropenia increases with the duration of acetaminophen use, and is greater in AIDS and low T4 at entry patients than in the high T4 at entry subgroup, but no attempt was made to assess relative timing of the two events. If neutropenia usually occurs first, acetaminophen use should not be implicated.

The sponsor's statement that acetaminophen, like AZT, is metabolized by glucuronidation and that competition for these enzymes by both drugs may limit the metabolism of AZT to its inactive metabolite, GAZT, and thereby result in higher plasma levels of AZT, is reasonable. Obviously, if AZT at these doses is this sensitive to the administration of another drug which is metabolized by the same enzyme(s), even though acetaminophen in these patients was often prescribed on an "as needed" (prn) basis, great care should be taken in the co-administration of other drugs which are glucuronidated, such as aspirin and sulfa drugs. Although no statistically significant differences in hematologic toxicity was seen in this study in patients who received other such drugs in addition to AZT, the study was not designed to investigate this possibility, and so negative findings are not particularly reassuring.

The sponsor states that they plan to analyze the effect of serum levels of AZT on hematologic toxicity, but this has not yet been submitted. Also, it does not appear that the sponsor examined the effect of co-administration of these drugs on efficacy parameters, except for acyclovir.

The co-administration of acyclovir (ACV) and AZT was examined by the sponsor because of recent in vitro evidence of the potentiation of the anti-HIV activity of AZT in combination with acyclovir. According to the sponsor, (see page 47 of this review) seventy (34 AZT and 36 placebo) of 282 patients enrolled in this trial received acyclovir in addition to their study medication. Of the 34 AZT patients, eleven received acyclovir for less than 2 weeks, 16 received ACV for 2 to 8 weeks, and 7 were treated with ACV for more than 8 weeks. According to the sponsor, there was no increase in hematologic toxicity in patients receiving acyclovir plus AZT compared to those receiving ACV alone. The sponsor apparently included patients who received less than 2 weeks of acyclovir in this analysis as well as patients on topical acyclovir only, and did not differentiate between those patients who developed hematologic toxicity before or after AZT administration.

The sponsor then calculated the incidence of OI's in these patients. They state that only 2 of 34 patients (6%) who received ACV in addition to AZT developed OIs over the course of the trial compared to 22 of 111 (20%) of the AZT recipients who did not receive acyclovir during the study. Because patients

were not randomly assigned to AZT or no AZT, reliable conclusions can not be drawn from this analysis. (Also, patients receiving AZT for less than 2 weeks and patients receiving the topical formulation were included in these data).

Further analysis of the possible effect of concomitant medications on the safety and efficacy parameters in this trial are warranted, but are unlikely to affect the strong statistical significance of the major efficacy parameters (deaths and incidence of OI's). Systematic clinical studies addressing the effects of potentially important drug interactions in patients taking AZT are needed.

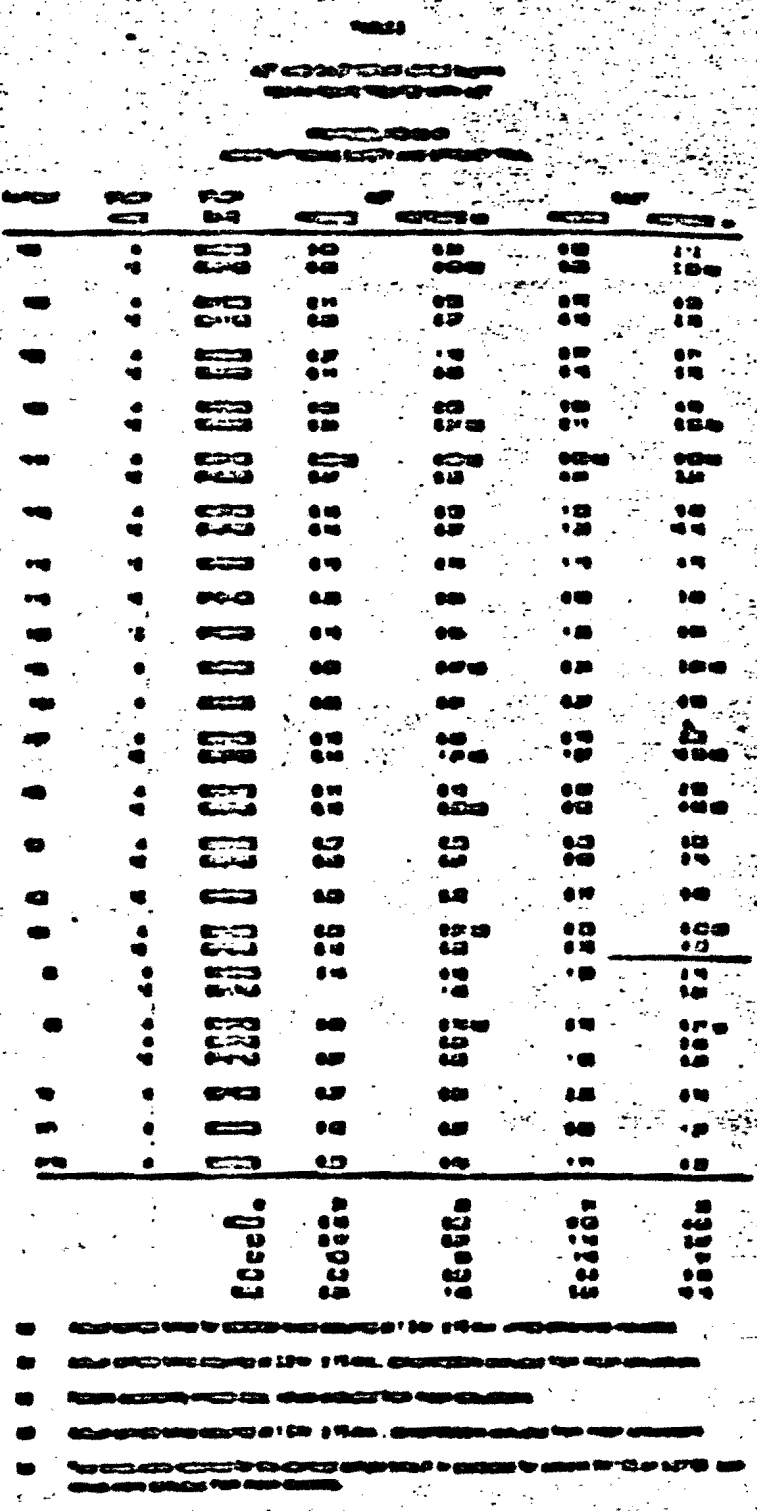
5) Deaths (as related to Safety)

Only one patient randomized to receive AZT died during the placebo-controlled portion of the trial, and this death was due to an opportunistic infection, cryptococcal meningitis at week 20 on trial, 10 days after discontinuing AZT and refusing treatment with antifungal medications. This was his second OI on the trial (PCP at 14 weeks). This patient had received RBC transfusions at weeks 16 and 20, but his lowest recorded neutrophil count 912 (at week 16). Thus it does not appear that the death was secondary to drug toxicity.

6) Serum levels of AZT

As indicated by the sponsor, peak and trough serum levels of AZT were obtained on the patients enrolled in one center (that of Margaret Fischl at the University of Miami). Samples were drawn just prior to a dose and 1.5 hr. after dosing in 21 patients receiving AZT at a dose of 250 mg q 4 h. Samples were obtained at 4, and 12 weeks in 12 patients, and at one time point in the other nine. The 1.5 hr. post-dose level was probably after the true peak in most patients, based on pharmacokinetic data from the Phase I trial (peak levels occurred 0.5 hours after dosing).

As related by the sponsor on page 56 of this review, mean (+ sd) predose postdose AZT levels of 0.15±0.17 and 0.60±0.33 ug/mL, respectively, were obtained. As is apparent from the variance around these numbers, there was a wide range of levels in the individual patients, which do not appear to be correlated to body weight, at least on an individual basis. In addition, postdose levels obtained in the same patient twice (e.g. at 4 weeks and 12 weeks) frequently varied by at least 2 fold in one direction or the other. (see Table 2 on following page). A more systematic attempt to collect pharmacokinetic data in patients of different weights on chronic dosing should be made.



7) Central Nervous System Evaluations

Data from cerebrospinal fluid examinations performed in patients demonstrating clinical signs and symptoms of neurologic disease were not analyzed by the sponsor for submission to the NDA. These data are potentially very valuable in providing information on the effect of AZT on neurologic complications of HIV infection, depending on how many patients actually had lumbar punctures during the study. Hopefully, the sponsor will summarize and analyze this data soon.

Formal neuropsychiatric testing using a battery of objective tests was performed on all patients, regardless of neuropsychiatric symptomatology, twice prestudy and every eight weeks during the treatment to measure cognitive and motor function. This data was analyzed by an outside consultant, Dr. Frederick A. Schmitt of the University of Kentucky Medical Center. A preliminary oral report was presented by Dr. Schmitt at the FDA Anti-Infectives Advisory Committee meeting on January 16, 1987, and a desk copy of a draft preliminary report provided to this medical officer. Dr. Schmitt states that "preliminary data analysis of both affective and cognitive measures obtained at weeks 8 and 16 suggest that patient's general level of affective functioning did not change .... AIDS and low T_4 patients receiving AZT showed a general reduction in the amount of distress experienced as a result of the affective symptoms reported .... More striking are the data reflecting cognitive functioning ... patients receiving AZT appeared to show improvements over baseline (not seen in placebo recipients) for attention, memory, visuo-perceptual, visual scanning, and mental and motor speed ... positive effects of AZT are most consistent for those patients with the AIDS diagnosis and those with low T_4 cell counts at entry ...."

The final formal assessment of this data is in preparation and will be submitted to the NDA. At that time it will receive a complete review by this medical officer.

Uncontrolled Studies

I. Sponsor's Summary of Phase I Pharmacokinetic and Tolerance Study

In addition to the multicenter, placebo-controlled study reviewed above, the sponsor submitted the results of an uncontrolled Phase I study initiated in July 1985, in support of this New Drug Application for AZT. This study was designed primarily as a pharmacokinetics and tolerance study but some potential measures of efficacy were also monitored. It was under this protocol that AZT was administered to humans for the first time. Most of the patients were enrolled at one center (National Cancer Institute under Dr. Samuel Broder and Robert Yarchoan), and at Duke University Medical Center under Dr. David Durack.

A. Study Design

The study was originally designed as an open rising single dose, multiple dose/multiple day (2-4 weeks) intravenous drug administration regimen. Initially, cohorts of 4-6 patients (with AIDS or advanced ARC) were enrolled sequentially beginning at a dose of 1 mg/kg every 8 hours.

When pharmacokinetic studies revealed adequate bioavailability of orally administered drug, the dosing regimen was amended to allow for four weeks of oral dosing to follow the intravenous therapy. The intravenous solution was mixed with orange juice or water for oral dosing until the capsule formulation was available (in November 1985). Pharmacokinetic studies were completed during both the intravenous and oral dosing periods at the following regimens:

Group	Intravenous Dose	Oral Dose	No. of Patients
A	1.0 mg/kg q 8 hr	2.0 mg/kg q 8 hr	4
B	2.5 mg/kg q 8 hr	5.0 mg/kg q 8 hr	6
C	2.5 mg/kg q 4 hr	5.0 mg/kg q 4 hr	7
D	5.0 mg/kg q 4 hr	10.0 mg/kg q 4 hr	7
E	7.5 mg/kg q 4 hr	15.0 mg/kg q 4 hr	5

All patients who tolerated AZT were eventually allowed to participate in long-term therapy through a second Phase I protocol (after the initial 6 weeks followed by a one month wash-out period in some patients).

To be eligible, patients were required to be a least 18 years of age and have CDC-defined AIDS or advanced ARC with unexplained weight loss > 10% or > 15 lbs or documented mucocutaneous candidiasis. Patients with ARC and patients with Kaposi's sarcoma as their only manifestation of AIDS were also required to be symtomatic and have an absolute T_4 count $< 500/mm^3$ and cutaneous anergy to four specified antigens.

Patients were hospitalized for the intravenous therapy (2-4 weeks) and were seen twice weekly as outpatients while on oral therapy during the

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the first 6 weeks of the study. Clinical and laboratory parameters were monitored closely. Blood was obtained for HIV culture biweekly. Lymphocyte subset analysis was done weekly, and skin tests placed monthly. For patients continued on extended therapy, similar parameters were followed on a somewhat less frequent basis. The sponsor summarized the data from this Phase I trial as of mid-September 1986 for the NDA.

1986?

B. Study Population

Thirty-three patients were enrolled into the Phase I AZT trial. Eight patients, including four who died, (as of mid-September 1986) are permanently discontinued . The continuing patients are being monitored at one of the following five centers:

1986 or 1985?

Investigator	Facility	No. of Patients
Dr. S. Broder	National Cancer Institute	22(6)*
Dr. D. Durack	Duke University Medical Center	5(2)*
Dr. J. Hamilton	Veterans Administration Hospital	1
Dr. H. Gottlieb	UCLA Medical Center	3
Dr. M. Fischl	Jackson Memorial Hospital	2

*(No. of patients who are permanently discontinued from the study.)

Twenty-nine of the 33 patients who were enrolled in the study were assigned to one of the five original intravenous/oral dose groups for pharmacokinetic studies. Twenty-one of these 29 patients continue to receive oral AZT according to a modified dosing regimen. The most recently enrolled patients (4) were entered into the second Phase I protocol and did not receive the initial intravenous dosing.

Demographic data at entry on the 33 patients is as follows: 32 males, 1 female; 22 AIDS, 11 ARC; ages 19-53 years with mean of 36.3 years; 28 were homosexual/bisexual.

The distribution of absolute T_4 counts at entry was as follows:

$<100/mm^3$	-	21/33	(16 AIDS + 5 ARC)
$100-500/mm^3$	-	11/33	(5 AIDS + 6 ARC)
$>500/mm^3$	-	1/33	(AIDS)

Seventeen of the 33 patients enrolled were known to have positive HIV cultures at entry.

Of the 22 AIDS patients, fourteen had recovered from PCP (including 4 who also had KS), 7 had KS without a history of OI, and one had a history of cerebral toxoplasmosis. The length of time between diagnosis of AIDS and entry into the study ranged from one month to 33 months with a mean of 8.8 months and a median of 5.5 months.

C. Study Drug

The study drug was supplied as a sterile filtered aqueous solution at a concentration of 20 mg/ml and as an opaque capsule containing 250 mg of AZT. The sterile solution was administered through an in-line micron filter as a one-hour infusion (each dose). The patients were scheduled to receive AZT, according to their assigned dose regimen for at least 6 weeks. The mean total daily intravenous dose for each dose group is presented below (initial 2-4 weeks of dosing only).

Group	Mean Total Daily Dose	Range
A	194 mg	167-216 mg
B	495 mg	300-635 mg
C	907 mg	672-1016 mg
D	2114 mg	1794-2415 mg
E	3344 mg	2372-4140 mg

Of the 29 patients in the pharmacokinetic study, all but the first 4 patients received only 2 weeks of intravenous therapy followed by 4 weeks of oral AZT at twice the intravenous dose. The majority of patients (25) consented to continue AZT therapy after completing the original 6-week dosing schedule. Chronic oral dosing was frequently modified for each patient according to their response to therapy (but not according to preset criteria). As of mid-September, 24 patients were continuing to receive AZT therapy according to the following regimens:

Oral Regimen	No. of Patients
500 mg q 4 hr	1
250 mg q 4 hr	5
250 mg q 6 hr	1
250 mg q 8 hr	11
250 mg q 12 hr	2
100 mg q 6 hr	3
100 mg q 8 hr	1

According to the sponsor, the total daily dose for these patients ranges from 300 to 3000 mg with a mean of 927 mg. Their daily dose in mg/kg ranges from 5.6 to 33.0 mg/kg with a mean of 12.8 mg/kg. Duration in the study for these patients (as of mid-September) ranged from 4-63 weeks with a mean of 33 weeks and median of 39 weeks (they may not have received AZT for the entire duration of their participation, however).

The highest dose of AZT tolerated to date is 1250 mg q 4 h (2 patients for 4 weeks). The highest dose tolerated for the longest period of time is 500 mg q 4 h (two patients for up to 20 weeks without toxicity). The dose regimen which has been administered continuously for the longest duration is 250 mg q 4 h. (One patients for 32 weeks without toxicity). As can be seen from the chart above, eleven of the 24 patients still on therapy (as of mid-September 1986) were on 250 mg q 8 h, with 6 at lower doses and 7 at higher.

D. Study Results

1) Pharmacokinetics

The pharmacokinetics and oral bioavailability of AZT in AIDS and ARC patients were evaluated according to the following schedule:

Group	Patients	IV Dose	Oral Dose
A	1 - 4	1.0 mg/kg q 8 hr (4)	2.0 mg/kg q 8 hr (3)
B	5 - 10	2.5 mg/kg q 8 hr (6)	5.0 mg/kg q 8 hr (6)
C	11 - 16	2.5 mg/kg q 4 hr (2)	5.0 mg/kg q 4 hr (3)
D	17 - 23	5.0 mg/kg q 4 hr (7)	10.0 mg/kg q 4 hr (5)
E	24 - 26	7.5 mg/kg q 4 hr (3)	15.0 mg/kg q 4 hr (1)

(n) = number of patients providing pharmacokinetic data

•Following the end of intravenous infusion, AZT plasma levels decayed biexponentially, indicating two-compartmental pharmacokinetics. The mean AZT half-life (t 1/2) at all dose levels following intravenous and oral administration was approximately 1.1 hour. AZT concentrations increased proportionally with intravenous and oral dosing within the range of 1.0 mg/kg q 8 h to 5.0 mg/kg q 4 hr and 2 mg/kg q 8 h to 10 mg/kg q 4 h, respectively, indicating dose-independent kinetics. However, a disproportional increase in peak concentration (Cmax) and area under plasma-concentration time curve (AUC) occurred between the 5.0 and 7.5 mg/kg q 4 h intravenous and the 10.0 and 15.0 mg/kg q 4 h oral dose levels.

•The major plasma and urinary metabolite was identified and characterized as 5'-glucuronyl azidothymidine (GAZT). The plasma levels of this inactive metabolite were approximately 2 to 3 times the corresponding AZT levels. GAZT was rapidly cleared from plasma with a half-life of 1.0 hour. Following intravenous AZT administration, approximately 20% of the dose is excreted unchanged in the urine and about 60% as GAZT.

•The bioavailability was approximately 65% following oral administration of AZT solution at doses of 2 mg/kg to 10 mg/kg. Based on urinary recovery data after oral dosing, the less than complete oral bioavailability is the result of first-pass metabolism rather than incomplete absorption. Peak plasma levels generally occurred at 0.5 hours after dosing, indicating rapid absorption.... There was no significant accumulation of AZT during the q 8 h dosing schedule.

"The bioavailability of the 250 mg AZT capsules was also evaluated during the Phase I study. Five patients receiving one to five 250 mg AZT capsules every 4 hours were studied. The extent of bioavailability of the 250 mg capsules ranged from 52 to 75% of the dose with a mean of 64±10% (comparable to that of AZT in solution). The mean time to peak plasma levels for the five patients receiving AZT capsules was 0.85±0.42 hours after dosing (slightly greater than after AZT solution taken orally).

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"AZT levels in cerebral spinal fluid have been evaluated for six patients being followed at the National Cancer Institute .... Overall, the data indicated that the CSF levels of AZT at steady state averaged 50% of plasma levels.

2) Safety

but the these were screened for tolerance for AZT.

"Nine of 29 patients who received intravenous therapy (4 for 4 weeks and 25 for 2 weeks) experienced hematologic adverse events (anemia, leukopenia, or neutropenia) while receiving intravenous AZT in all 5 dose groups. The definition of anemia, leukopenia, and neutropenia varied among the five investigators. Six required red cell transfusions. AZT was temporarily discontinued in two cases and permanently discontinued in two patients after development of anemia. Five of the patients developed leukopenia and four developed neutropenia.

"Five patients experienced neurologic/psychiatric adverse events during intravenous AZT administration (including two patients with headaches). Each patient was in a different intravenous dose group. Two of the patients experienced anxiety reactions after 12-19 days on therapy and AZT was permanently discontinued. The fifth patient experienced a severe dystonic reaction which was successfully treated with Benedryl and Valium and did not recur during 7 additional days of AZT. One additional patient experienced nausea and vomiting which required treatment.",

a) Oral Administration of AZT (during the six week pharmacokinetic study)

"Adverse experiences most frequently reported during the 6 week dosing period included hematologic and neurologic events .... after 4 weeks of dosing, there was a mild (approximately 1 gm/dl) decrease in hemoglobin across all dose groups. At week four, the absolute neutrophil count had decreased in the 5.0 mg/kg q 4 h I.V./10 mg/kg q 4 h oral dose group, returning to normal by 6 weeks. Platelet counts gradually rose in all five dose groups."

Neurologic/psychiatric events developed in three additional patients during the oral phase of the 6 week pharmacokinetic study. A sixth patient complained of feeling "spacey" and anxious but no treatment was required and symptoms resolved on AZT. Similarly a mild headache and a severe headache in two additional patients resolved on continued AZT without specific treatment.

Clinical evaluation included daily to weekly assessments of several subjective symptoms. According to the sponsor, the most frequently reported symptoms included mild to moderate fatigue (10 of 28 patients) and headache (17 out of 28 patients).

"In general, intravenous and oral administration of AZT during the 6 week pharmacokinetic study was well tolerated. No patient developed hepatic, renal or cardiac dysfunction that could be attributed to AZT. The most frequently reported adverse experiences were hematologic in nature. Seven patients received red blood cell transfusions in response to possible drug related anemia."

b) Safety and Tolerance of Chronic Oral Administration of AZT

"After completing the original 6 week dosing schedule, twenty-five patients consented to continue an additional 6 to 12 months of oral AZT therapy. Four new patients (who did not received the initial intravenous dosing) were entered into the trial subsequent to the 6 week pharmacokinetic study .... Chronic oral AZT dosing was frequently modified for each participant according to their response to therapy...

"The most frequently reported adverse experiences during the extended dosing period were hematologic in nature and consisted of leukopenia, neutropenia, anemia, thrombocytopenia, and increased mean corpuscular volume .... It is difficult to correlate development of anemia or other hematologic abnormalities to a specific dose regimen or chronicity of dosing due to significant variability among the participants in terms of dosing and duration of therapy. However, hematologic abnormalities may be related to dose and duration of therapy on an individual basis .... In many cases, hematologic toxicity was not characterized as a single abnormal parameter; rather, patients would develop anemia in conjunction with leukopenia, neutropenia, or thrombocytopenia .... This suggests bone marrow depression by AZT. Five of the patients in the Phase I study had one or more bone marrow examinations performed .... The overall cellularity of the marrows was described as ranging form normal to moderately hypocellular. Several of the marrows showed marked erythroid hypoplasia accompanied by a maturation defect presumed to be megaloblastic .... Eleven out of twenty-one patients had documented elevated mean corpuscular volumes (MCV) during the extended dosing period ....

"In all cases of permanent discontinuation of AZT therapy, when hematologic abnormalities were present, additional events such as progression of Kaposi's sarcoma, onset of serious opportunistic infection, overall deterioration in clinical status, or patient request for removal from the study, contributed to the decision to withdraw AZT therapy.

"Seven patients developed laboratory evidence of liver function abnormalities during the course of AZT administration." None were clearly related to administration of AZT.

"Three neurologic/psychiatric events were reported during the extended dosing period: mild disorientation and difficulty concentrating in one patient which resolved while on the same dose of AZT; abrupt onset of expressive aphasia, ataxia and tremors in another patient which resolved within 24 hours of hospitalization; complaints of feeling anxious and 'spacey' in another patient on two occasions, not requiring treatment. Another patient complained of difficulty concentrating and a fifth reported insomnia, anxiety and a feeling of 'numbness', but these events were not reported as adverse drug experiences. None of these patients were permanently discontinued from AZT because of neuropsychiatric complaints.

"Twenty-five out of thirty-one patients reported mild to severe fatigue at some point during extended dosing. The severe fatigue was reported by three patients, with deteriorating clinical conditions, prior to their death. Malaise and lethargy (21 and 22 patients, respectively) were the second most frequently reported symptoms followed by loss of appetite (18 patients). Many of these symptoms were present prior to enrollment in the study."

In summary, the sponsor states: "The most common adverse events, which are considered probably related to study drug (or the relationship was unknown), were hematologic abnormalities, particularly anemia, leukopenia and neutropenia .... for many of the patients who developed hematologic adverse experiences, a tolerated dose of AZT was established after modification of dosing or temporary discontinuation of study drug .... once a tolerable AZT dose was determined for a patient, the number of hematologic events decreased for that individual."

3) Sponsor's Analysis of Efficacy (of Phase I study)

"The original Phase I study was designed to include the monitoring of a number of potential measures of clinical response, with the understanding that no definitive answers regarding efficacy could be determined in the absence of a control group. The 'efficacy' measures included improved clinical status (e.g. weight gain), elimination of virus or decrease in the amount of detectable virus, and improvement in parameters of immune function (e.g. increased in absolute number of T-helper cells and reactivation of delayed cutaneous hypersensitivity skin tests). Some parameters, such as onset of opportunistic infections, were identified retrospectively as possible measures of efficacy and were entered into the evaluation of clinical response. All efficacy parameters were monitored during the 6 week pharmacokinetic study and continued during chronic oral AZT dosing."

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a) Clinical Response Following 6 Weeks of AZT Dosing

1. Clinical Status

"Twenty-nine AIDS and ARC patients participated in the original pharmacokinetic study. Some improvements in clinical status were observed in these patients. Thirteen out of 18 AIDS patients had weight gains which ranged from 1.0 kg to 7.0 kg with a mean of 3.3 kg following 6-8 weeks of AZT dosing. Six out of ten ARC patients had weight gains ranging from 1.0 kg to 10.0 kg with a mean of 5.3 kg.

"Several patients reported resolution of a number of HIV infection associated symptoms such as malaise, fatigue, loss of appetite, nausea, etc .... Six patients reported resolution of fevers or night sweats or significant improvement in their sense of well being. In addition, two patients had spontaneous clearing of nailbed fungal infections and one patient had an improvement in severe debilitating aphthous stomatitis in the absence of specific therapy. Neurologic improvements were observed in two patients. One patient had spontaneous clearing of peripheral neuropathy which included lower extremity weakness and dysesthesia .... Another patient, with HIV associated dementia, had substantial improvement in mentation following 6 weeks of AZT dosing .... When AZT was withdrawn, the patient's mental function deteriorated."

2. Immune Function

"Twenty-five out of 27 patients were anergic at entry into the study .... Following approximately 6 weeks of AZT dosing, 6 out of 17 AIDS patients and 3 of 8 ARC had a positive response to one or more skin test antigens, all of whom also had an increase in their number of T-helper cells during the same period.

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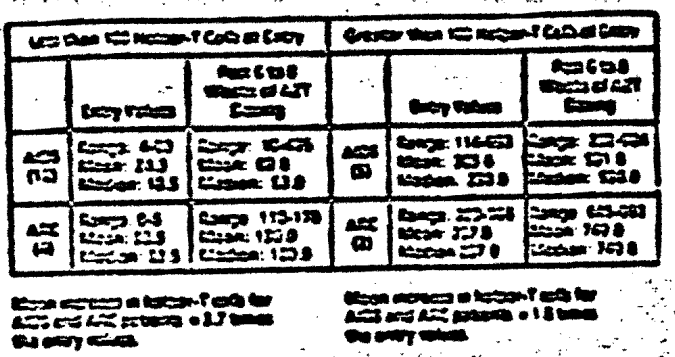
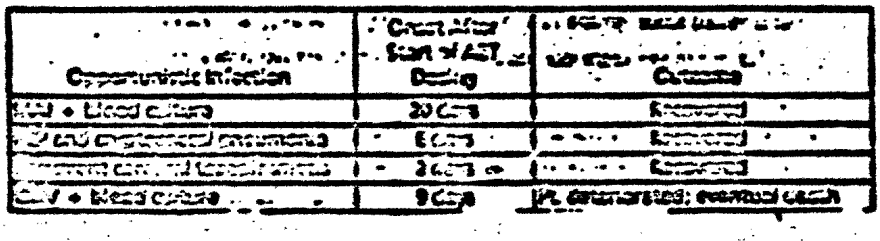
"Overall, a total of 23 of the 23 patients with baseline values had an increase in helper T-cells after approximately 6 to 8 weeks of AZT dosing, summarized in the Table below.



Helper T-cell values for the "off drug" period immediately following the initial 6 weeks of AZT dosing are available for 13 of the 23 patients who had an increase in helper-T cells. In all 13 cases, the number of helper-T cells decreased during the off drug period.

3. Opportunistic Infections

Four patients developed opportunistic infections during the initial 6 weeks of AZT dosing, summarized in the chart below



The first and third patients continued on AZT while being treated for their OI and the second had AZT temporarily discontinued due to anemia.

4. Antiviral effect

"Analysis of the blood samples collected weekly to biweekly for HIV culture has not been completed.

"Bioassay results for α-interferon levels during the initial 60 to 8 weeks of AZT dosing are available for 6 patients, five of whom had positive titers (>12 IU/ml) at entry. Following 6 to 8 weeks of AZT, four of these five patients had negative (<4 IU/ml) α-interferon titers, suggesting the possibility of a drug effect.

"In summary, following 6 to 8 weeks of AZT dosing, some patients had measurable improvement in a number of potential measures of clinical response .... In the absence of a control group, these positive clinical and immunologic responses could not be definitely attributed to AZT administration ... in the absence of life-threatening toxicity ... improvements ... were sufficient enough to warrant continued AZT dosing.

b) Clinical Response During Chronic Oral AZT Dosing

1. Clinical Status

Twenty-five of 29 patients elected to continue chronic AZT treatment after completing the 6 week pharmacokinetic study and an additional four patients were enrolled into the second Phase I protocol. As of mid-September, 1986, twenty-four patients were receiving chronic oral AZT therapy. Their dose regimens vary from 250 mg q 12 h to 100 mg q 4 h.

the 4 who died were replaced

During chronic oral dosing, 6 of 11 ARC patients and 8 of 18 AIDS patients gained weight or maintained weight which was acquired during the initial 6 weeks of dosing. The remainder experienced a net loss in weight.

One patient had significant improvement in HIV associated neurologic dysfunction after receiving 8 weeks of AZT therapy at a dose of 250 mg q 4 h. Some patients have reported recurrence of chronic HIV infection associated infections such as fungal paronychia and herpes simplex and herpes zoster infections. Five patients developed bacterial or possible bacterial infections during the extended dosing period, all of whom responded to antimicrobial therapy while AZT was continued (except for one patient).

2. Immune Function

Delayed hypersensitivity skin test responses for patients anergic at entry are summarized in the following Table.

Delayed Hypersensitivity Skin Test Response to One or More Antigens

Entry	Following Initial 6 Weeks of Dosing	During Chronic AZT Administration	No. of Patients
-	+	+	5
-	+	-	1
-	-	+	4
-	-	-	11

The mean helper-T cell values for the 28 patients at entry and during chronic AZT administration are presented below.

[illegible]
[illegible]

Patients with ↑ Number of Helper-T Cells			Patients with ↓ Number of Helper-T Cells		
	Entry Values	During Chronic Dosing		Entry Values	During Chronic Dosing
[illegible]	Range: [illegible] Mean: [illegible] Median: [illegible]	Range: [illegible] Mean: [illegible] Median: [illegible]	[illegible]	Range: [illegible] Mean: [illegible] Median: [illegible]	Range: [illegible] Mean: [illegible] Median: [illegible]
[illegible]	Range: [illegible] Mean: [illegible] Median: [illegible]	Range: [illegible] Mean: [illegible] Median: [illegible]	[illegible]	Range: [illegible] Mean: 141.3 Median: 157.5	Range: 5-151 Mean: 61.8 Median: 52.5

"In summary, 10 out out of 23 patients were able to either sustain or acquire an increase in absolute number of helper-T cells during administration of AZT, and eighteen patients had a decrease in helper-T cells, thirteen of them were known to previously have an increase in helper-T cells following the initial 6 weeks of AZT dosing. It is difficult to correlate the increase or decrease in absolute number of helper-T cells to AZT dose or chronicity of dosing as each patient's dose regimen and duration of therapy were quite variable.

3. Opportunistic Infections

Nine out of 29 patients developed OI's during or following chronic AZT administration (excluding OI's during the first 6 to 8 weeks of dosing). In 6 of these cases the OI was PCP, some of which were fatal. Only one case of an OI was fatal and this was pneumonia which occurred in a patient 13 weeks after AZT therapy was discontinued voluntarily. Progression from ARC to AIDS occurred in 2 patients.

4. Kaposi's Sarcoma

"Eleven AIDS patients entered the study a diagnosis of Kaposi's sarcoma. One patient is reported to have stable disease, one had a complete resolution of lesions, 3 had partial resolution of lesions, and 6 patients have had mild to severe progression their KS.

5. Antiviral Effect

"Blood samples were collected every 4 to 12 weeks for HIV culture during chronic AZT administration. Analysis of these data have not been completed."

"In summary, some of the patients who were continued on oral AZT therapy were able to maintain positive clinical responses which were observed after the initial 6 weeks of dosing. Four patients have died (as of mid-September 1986) since the trial was initiated; one of progressive visceral KS fourteen weeks after AZT was discontinued after 4 weeks of dosing; one died of cryptococcal meningitis 13 weeks after AZT was discontinued secondary to overall deterioration in his clinical status after 20 weeks of AZT; a third patient died of bilateral pneumonia (pathogen not identified) 5 weeks after AZT was voluntarily withdrawn after 24 weeks of therapy, due to deteriorating clinical condition; the fourth patient expired after cardiopulmonary arrest secondary to bacterial pneumonia, dementia, and HIV infection, two weeks after drug was discontinued due to onset of anemia, thrombocytopenia, and leukopenia.

"In conclusion, the pharmacokinetics of AZT were established during this Phase I study. AZT was demonstrated to have good bioavailability after oral administration and was shown to penetrate the blood-brain barrier... The most significant toxicity associated with AZT dosing was probable bone marrow suppression identified by onset of anemia, neutropenia, and leukopenia. Some patients had measurable improvement in a number of potential measures of clinical response including weight gain, resolution of HIV infection associated symptoms such as fatigue and night sweats, and improvement in HIV-associated neurologic dysfunction... In the absence of a control group, these positive clinical and immunologic responses could not be definitely attributed to AZT administration...but were sufficient to warrant additional controlled clinical studies."

(178

Reviewer's Analysis of Phase I Uncontrolled Trial

As noted in the sponsor's summary, this trial was initially planned as a "classic" Phase I dose-escalating pharmacokinetics and safety study of a new drug to be administered to humans for the first time. It was different from many Phase I studies, however, in that the patients were all high risk, with AIDS or advanced ARC, and the drug was administered indefinitely if tolerated.

The results of the pharmacokinetic studies in this Phase I trial are summarized adequately by the sponsor (see preceeding pages of this review). Briefly, the results demonstrated two compartmental pharmacokinetics with biexponential decay. The half-life after intravenous or oral administration is slightly longer than an hour without "significant accumulation during the q 8 h dosing schedule." AZT is well absorbed after oral administration with approximately 65% bioavailability compared with intravenous administration.

Penetration into the cerebrospinal fluid (CSF) varied with the dose in the six patients in whom CSF levels of AZT were obtained (see table on page 125). At the doses used in the Phase II efficacy trial (3-5 mg/kg/dose orally), the CSF/plasma ratios in the two patients who received doses in this range were 0.15 and 0.20. At higher doses (the equivalent of 10-15 mg/kg orally), CSF penetration of AZT was much better in the four patients tested, but these doses are clearly in excess of what can be tolerated in most patients with AIDS or advanced ARC. Also information regarding their clinical status and neurologic functioning at the time of lumbar puncture was not submitted; these six patients presumably all had neuropsychiatric symptoms which prompted their lumbar punctures. These data may be important in the analysis of AZT levels in the CSF, as penetration of any drug into the central nervous system is in part correlated to the tissue damage and inflammation at the "blood brain barrier."

? useless CSF levels
3-5 mg/kg

CSF Penetration of AZT™

Patient ID	Dose (mg/kg)	Route	Sample* Time (hr)	AZT in CSF (ug/ml)	CSF:plasma Conc. Ratio
18	5		2	0.38	0.67
22	5		4	0.23	0.73
16	5		4	0.10	0.53
12	2.5-5		3.7	0.13	0.20
				MEAN ± SD	0.53 ± 0.24
01	2		1.8	0.04	0.15
26	15		4	0.62	1.35

*Hours after start of last dose.

The question of whether AZT accumulates after q 4 h dosing can best be answered by examining plasma levels from the placebo-controlled trial (see page 107 of this review).

The major plasma and urinary metabolite was identified as 5'-glucuronyl azidothymidine which has no activity against HIV in vitro and is rapidly cleared from the plasma.

The toxicity of AZT seen in the Phase I trial was basically predictive of that seen later in the placebo-controlled Phase II trial, i.e. anemia, leukopenia and neutropenia. These hematologic adverse events were felt to be drug related but not particularly dose related in the group as a whole. Transient neuropsychiatric events were also reported in several of the patients and nausea and vomiting requiring treatment in one. Patients with severe anemia were frequently transfused and continued on AZT, usually at a reduced dose, although in two patients AZT was permanently discontinued because of anemia. Neutropenia was more often the dose-limiting adverse event. The highest dose administered was 7.5 mg/kg q 4 h for 2 weeks (four patients) followed by 15 mg/kg P.O. q 4 h. All but one of these patients were then dose reduced due to hematologic toxicity. The one who tolerated 1250 mg po q 4 for four additional weeks was reduced to 500 mg po q 4 h "per protocol."

As noted by the sponsor, several parameters of efficacy were also monitored during the Phase I trial, including weight gain, symptoms, general clinical status, and selected immune parameters such as delayed hypersensitivity skin tests and T-helper cell counts. Improvements in these parameters were observed in a number of patients.

Phase I toxicity

Twenty-five of the 29 patients enrolled in the initial 6 week trial elected to continue taking AZT under an extension protocol. Four additional patients were enrolled directly into the extended dosing protocol. As of mid-September, 24 patients were receiving AZT at doses ranging from 300 mg/day to 3000 mg/day with eleven at 250 mg q 8 h (see chart on page 112 of this review) and 4 patients had died. Nine of the 29 patients developed OI's during or following chronic oral dosing (excluding those which developed during the initial 6-8 weeks of therapy). Some of the difficulties in assessing the possible significance of these clinical observations in relation to AZT include the heterogeneity of the patients (all stages of AIDS/OI, AIDS/KS, and advanced ARC), the varying dosage regimens used, and the frequent dose interruptions and/or reductions due to hematologic toxicity in nearly all of the patients.

Follow-up data from this trial was submitted as part of an amendment to the NDA on January 12, 1987. The sponsor relates that an additional seven patients died between mid-September and December 31, 1986 for a total of eleven deaths among Phase I participants. Of the seven recent deaths, two occurred in patients who had been off the protocol for over 11 months. One additional death was an apparent suicide in a motor vehicle accident of a patient with AIDS who had been on AZT intermittently for almost a year with frequent dose reductions and temporary discontinuations due to severe anemia. (In August 1986 he was transfused on one occasion with 8 units of packed RBC for a hematocrit of 10.8). He was receiving 250 mg q 8 h when he died. The other four patients died of complications of AIDS while still receiving AZT or shortly after being discontinued due to deterioration.

As of December 31, 1986, eighteen of the 33 Phase I participants were still receiving AZT, only six of whom were still tolerating a dose of 250 mg q4h (including one at 500 mg q4h). The remaining twelve patients had died, or had been dose reduced or discontinued.

Although a more heterogenous group of patients were enrolled in the Phase I study than in the placebo-controlled trial, and the dosing was more varied, the current mortality in the Phase I study (over half the patients still alive after 12-18 months of therapy) provide additional data supporting the efficacy of AZT in patients with AIDS and advanced ARC.

Labeling Review

The proposed labeling submitted by the sponsor in Volume 2.2 of the NDA has been extensively revised during the past two weeks in a series of meetings in which the representatives of the various reviewing displicines in the Division of Anti-Infective Drug Products participated, including this medical officer. The medical officer concurs with the contents of this revised draft labeling, a copy of which is attached to this medical review. This draft is included in lieu of a detailed written review of the sponsor's proposed labelihg.

Summary and Conclusions

(1) Zidovudine is an analogue of the nucleic acid thymidine with the substitution of an azido group (- N_3) for the hydroxyl group (-OH) at the 3' position; hence its chemical name,3'-azido-3'deoxythymidine, commonly referred to as azidothymidine (AZT). Zidovudine is an inhibitor of the human immunodeficiency virus (HIV) in vitro at concentrations ranging from <0.13 ug/ml (ID_{90}) when added shortly after laboratory infection of susceptible cells, to >10.0 ug/ml for "partial" inhibition of viral replication in chronically infection cell lines (presumed to carry HIV DNA integrated into the host cell genome). These data suggest that zidovudine may work in vivo by inhibiting the spread of infection to susceptible uninfected cells, but may do little to inhibit viral replication in previously (chronically) infected cells. However, the relationship between concentrations of zidovudine required to inhibit viral activity in vitro and plasma levels that are necessary for clinical efficacy are unknown.

(2) The mechanism of action of zidovudine against HIV appears to be the following: zidovudine is converted into zidovudine monophosphate by cellular thymidine kinase, to zidovudine diphosphate by the cellular enzyme thymidylate kinase, and to zidovudine triphosphate by other cellular enzymes, as yet unidentified. Zidovudine triphosphate inhibits the activity of the HIV DNA polymerase enzyme (reverse transcriptase) which is essential for viral replication. Zidovudine also inhibits cellular α-DNA polymerase, but to a much lesser degree. Zidovudine triphosphate can also be incorporated into DNA which then terminates further chain elongation.

(3) Zidovudine has been shown to inhibit some other mammalian retroviruses in vitro, but has no significant antiviral activity against a variety of other human and animal viruses, including herpes simplex virus type 1, cytomegalovirus, adenovirus type 5, coronavirus, influenza A virus, respiratory syncytial virus, measles virus, rhinovirus IB, bovine rotavirus, and yellow fever virus. It has been shown to inhibit the replication of Epstein Barr virus (EBV) with an ID_{50} of 1.4 to 2.7 ug/ml, although the clinical significance of this finding is unknown.

Some gram-negative bacteria, in particular members of the Enterobacteriaceae family (including Shigella, Salmonella, Klebsiella, Enterobacter, Citrobacter, and E. coli), are inhibited by low concentrations of zidovudine (0.005 to 0.5 ug/ml). Giardia lamblia, an intestinal protozoan pathogen, is inhibited by 1.9 ug/ml. There is no significant activity against other protozoa, fungi, mycobacteria, and gram positive or anaerobic bacteria which were tested. Thus, it would appear that zidovudine exerts its beneficial effects in HIV-infected individuals directly through its antiretroviral activity, and not indirectly by inhibiting one or more opportunistic organisms. The possible contribution of its activity against EBV in HIV-infected patients in whom actively replicating EBV can often be detected is unknown.

(4) It is not known at this time whether zidovudine-resistant strains of HIV exist in the general population or how rapidly resistant strains may emerge in infected individuals receiving chronic zidovudine therapy. It is known that there are many different strains of HIV defined by antigenic determinants; whether there is a range of susceptibility to reverse transcriptase inhibitors such as zidovudine is unknown.

(5) During the initial Phase I uncontrolled study, zidovudine was administered to AIDS and ARC patients in intravenous, oral solution, and 250 capsule formulations and provided the following information on pharmacokinetic parameters. The half life of zidovudine is approximately one hour. Peak concentrations occur between 30 and 90 minutes depending in part on the formulation and route of administration. The oral formulations are essentially completely absorbed with bioavailability compared to the intravenous formulation averaging 65% (approximately one third of the dose is removed by first-pass metabolism in the liver before it reaches the systemic circulation). Zidovudine is rapidly metabolized by glucuronidation to 3'-azido-3'-deoxy-5'-O--D-glucopyranuronosylthymidine (GAZT), which has no demonstrable antiviral activity. Urinary recovery after oral administration consists almost entirely of unchanged drug (14%) and GAZT (74%).

In the Phase II efficacy trial, a subset of patients at one of the centers had peak and trough levels of zidovudine obtained while on chronic therapy at 250 mg q 4 h. The mean serum concentrations observed were 0.62 ug/ml (1.5 hours post-dose) and 0.16 ug/ml (predose). There was no evidence of drug accumulation with chronic dosing.

(6) Zidovudine appears to cross the blood brain barrier. Cerebrospinal fluid (CSF) concentrations of zidovudine were measured in six patients from the Phase I trial receiving doses ranging from 2 mg/kg p.o. to 10 mg/kg . There was a clear dose effect seen in the CSF/plasma ratios which ranged from .15 at the lowest dose to 1.35 at the highest dose. Only a single CSF sample was obtained in each patient. More extensive studies of the ability of zidovudine to penetrate the central nervous system are needed.

(7) The efficacy of zidovudine was demonstrated in a single placebo-controlled trial conducted in the United States last year in which two hundred and eighty-one (281) immunosuppressed patients with AIDS/past PCP or advanced ARC were enrolled at 12 centers across the country over a period of 4 months. Patients were randomized to receive either placebo or zidovudine at a dose of 250 mg every 4 hours. The study was planned to continue for at least 24 weeks, but was ended early in September 1986, after a median duration on therapy of 18 weeks, due to a highly significant reduction in mortality in the group receiving zidovudine compared to the group receiving placebo. At that time, all patients were offered the option of receiving zidovudine at a dose of 200 mg every four hours in an uncontrolled open-label extension of the trial.

In addition to the reduction in mortality observed at the end of the placebo-controlled portion of the trial (19 deaths in the placebo group and one in the zidovudine group), a significant reduction in the risk of acquiring an AIDS-defining OI after the first 6 weeks of therapy was also demonstrated. In addition, patients receiving zidovudine tended to maintain their body weight and functional performance status, whereas placebo patients showed a net decline in these parameters. A statistically though probably not clinically significant increase in peripheral T-helper cell counts and cutaneous hypersensitivity skin testing was also observed in the group receiving zidovudine compared to the group on placebo.

(8) The difference between the treatment groups in the major efficacy parameters (death and risk of developing an AIDS-defining opportunistic infection) in the placebo-controlled trial was demonstrated in the group of patients with T-helper cell counts at entry of less than 200/mm^3. Seventy-eight percent of all the patients enrolled in the trial had a mean T_4 count under 200/mm^3 at entry (55% of the 160 AIDS patients and 56% of the 121 ARC patients). Although the inclusion criteria for enrollment in the trial allowed patients with T_4 counts as high as 500/mm^3 to be entered, and the patients were pre-stratified and randomized on the basis of entry T_4 count greater than or less than 100/mm^3, an early examination of the data indicated that virtually all of the "significant events" (deaths and OI's) occurred in patients with entry T_4 counts less than 200/mm^3 and that virtually all of the AIDS and most of the ARC patients who were enrolled had fewer than 200 T_4 cells/mm^3 anyway. These facts, along with a general consensus in the medical community and scientific literature that the absolute T-helper cell count in the peripheral blood of HIV-infected individuals is the most reliable predictor of later progression to more advanced stages of disease, particularly after T_4 counts drop below 200/mm^3, provide the basis for the recommendation to restrict approval of zidovudine at this time to symptomatic HIV-infected patients with a T-helper cell count less than 200/mm^3.

An adequate number of patients with T_4 counts greater than 200/mm^3 were not studied for a sufficiently long period of time in the placebo-controlled trial to determine the risk:benefit ratio of the drug is effective in this less immunocompromised group of patients. Of particular concern is the possibility that the hematologic toxicity of the drug when administered over a prolonged period of time may eventually debilitate patients to such an extent that they may become less able to resist opportunistic infections and other complications of HIV-disease than if they had been left untreated.

(9) The major toxicities observed in the placebo controlled trial were hematologic. Significant (>2 gm/dl) declines from baseline hemoglobin levels occurred in over 10% of patients on zidovudine as early as the third week of therapy and were seen in one third of the patients by 6 weeks of therapy. Thirty-one (31%) percent of all AZT recipients (11% of placebo recipients) received at least one transfusion during the placebo-controlled trial, and 21% required multiple transfusions (compared to 4% of placebo recipients). The need for transfusions was concentrated in the more advanced patients with 46% of the AIDS patients on zidovudine receiving at least one RBC transfusion (compared to 10% of ARC patients) and 40% of patients with entry T_4 100/mm^3 (compared to 15% of patients with entry T_4 100/mm^3).

Neutropenia was also common in patients receiving zidovudine. Granulocyte counts dropped below 1000/mm^3 in fifty-five (55%) of zidovudine recipients, below 750/mm^3 in 35%, and below 500/mm^3 in 16% at some time during the trial (comparable percentages of placebo patients were 22%, 7%, and 2%, respectively). Neutropenia was also more commonly observed in the more advanced patients than in the less advanced ones, with 50% of zidovudine recipients with AIDS or a T_4 count 100/mm^3 experiencing declines in absolute neutrophil counts to less than 750/mm^3 at some time during the trial compared to 25% of ARC patients and 19% of those with a T_4 count 100/mm^3 at entry. Over a third (51/144) of zidovudine recipients had at least one dose modification (dose reduction, temporary discontinuation, or permanent discontinuation) for hematologic toxicity compared to 7/135 (5%) of the placebo recipients.

Statistical regression analysis performed by the sponsor indicated that the T_4 cell number at entry was associated with the later development of anemia, and that entry hemoglobin, neutrophil count, T_4 cell number, and vitamin B12 levels were all associated with later decreases in absolute neutrophil count to less than 750/mm^3.

(10) An aspect of the efficacy analysis which requires more detailed attention is the effect of dose reductions and interruptions of therapy on the risk of acquiring opportunistic infections. This risk is difficult to assess because dose modifications were generally made after significant hematologic toxicity had already developed, and because dose modifications did not follow a set of uniform criteria. It may be impossible to determine

whether an increased number of OI's in patients who had dose modifications was due to subtherapeutic levels of zidovudine, or whether these patients were more prone both to OI's as well as to the toxicity of zidovudine because of a third factor such as the severity of their underlying disease.

(11) Most of the patients in the study received other systemic medications in addition to zidovudine or placebo at some time during the trial. The effect of administration of acyclovir, trimethoprim-sulfamethoxazole, pyrimethamine, other sulfa containing compounds, aspirin-containing products, acetaminophen-containing drugs, and ketoconazole were examined to evaluate possible potentiation of hematologic toxicity. According to the sponsor's analysis, only acetaminophen was associated with any potentiation of marrow suppression in that patients who took acetaminophen had a greater risk of developing low neutrophil counts ($p=.03$) than zidovudine recipients who did not take acetaminophen-containing products; the risk appeared to increase with duration of acetaminophen use. While this observation needs confirmation in an appropriately designed trial, it is not a surprising finding in that acetaminophen is known to be glucuronidated in the liver, and possible competition for the enzymes which glucuronidate zidovudine was hypothesized at the time the metabolism of zidovudine in humans was established shortly after the Phase I trial began.

(12) Adverse events reported during this controlled trial were common (at least one adverse experience was reported in 84% of the zidovudine recipients and in 72% of the placebo recipients). Presumably many of these adverse events were clinical manifestations of the underlying disease itself. In the analysis of all patients, nausea, myalgia, and insomnia were reported significantly more frequently in zidovudine recipients compared to placebo recipients. Of these three events, only nausea was convincingly associated with zidovudine administration, both in terms of the proportion of patients who reported it (46% of zidovudine recipients vs. 18% of placebo recipients) and the significance of the difference ($p<0.001$).

Clinical adverse experiences which occurred in more than 10% of the patients overall were anorexia, asthenia, diarrhea, fever, headache, nausea, abdominal pain, and rash. Of these, nausea and severity of headache appeared related to zidovudine administration.

(13) It is clear from both in vitro studies and the clinical trials that zidovudine does not eliminate HIV from the body of infected individuals. The best that can be anticipated is that by inhibiting active viral replication and infection of previously uninfected susceptible cells, progressive destruction of target tissues, including lymphocytes, macrophages, and neural tissue, may be halted, possibly accompanied by some "spontaneous" recovery of the immune system. There is no reason to believe that the antiviral effect of zidovudine will persist if therapy is withdrawn, and therefore it would appear that it must be taken for life.

Another consequence of the persistence of virus in the body despite zidovudine therapy is that the potential for transmission of the virus to others through sexual contact and/or inoculation of contaminated blood remains.

(14) All of the pre-clinical animal toxicology studies normally completed at the time a drug is approved for marketing have not been performed as yet with zidovudine. Regarding studies of chronic exposure in animals (two species), only the three and six month studies have been completed, and, one of them, the six month study in monkeys has not yet been submitted to the FDA for review. Twelve-month chronic toxicity studies have only recently been initiated; the same is true of the carcinogenicity studies. Animal studies designed to assess the effect of zidovudine on reproduction including fertility and teratogenicity have not been completed.

Because of the pressing need for an effective therapy in AIDS, even if the benefits are limited, zidovudine will be approved without the knowledge these normally required pre-clinical studies would provide. Chronic toxicity and carcinogenicity studies are of particular value in a situation where people will be taking the drug for years.

(15) A preliminary examination of data (deaths and opportunistic infections) collected from the uncontrolled portion of the trial beginning in late September, 1986, revealed the following:

a) The patients originally assigned to zidovudine who are continuing to receive the drug have been experiencing opportunistic infections at a higher rate since the trial ended than during the initial 6-18 week period on therapy which occurred during the placebo-controlled portion of the trial. The majority of OI's are Pneumocystis carinii pneumonia (PCP). Eleven more patients have died (including two suicides) during the 16-20 weeks of open-label zidovudine therapy as of February 13, 1987.

b) The patients originally assigned to placebo have received a total of 18-20 weeks of zidovudine therapy as of February 13, 1987. Twelve additional deaths have occurred in patients after beginning treatment with zidovudine, seven of which occurred in the first month of treatment. The incidence of OI's during this first month was similar to what it had been on placebo. The risk of developing an OI declined after 4-6 weeks of zidovudine treatment, as it had after a similar period on drug in the original zidovudine group. The actual incidence of OI's and deaths is higher in the original placebo group during the 6-18 week interval on zidovudine than it had been in the original zidovudine group during that period in the placebo-controlled trial; this is not

unexpected since the original placebo group were at a more advanced stage of disease when they began treatment with zidovudine than were the original zidovudine group.

c) Tentative conclusions that appear valid from the preliminary analysis of this data appear to be as follows:

During the first 4-6 weeks of treatment with zidovudine the risk of developing an OI appears similar to that which occurs in the absence of zidovudine treatment. After 6 weeks, the risk of developing an OI is reduced for the following 12 weeks of treatment (in patients with AIDS/post PCP or advanced ARC). After 18 weeks of therapy, the risk of OI's (and death) appears to increase again in patients on zidovudine but it is unclear whether this increased risk is similar to what it would be without treatment, since a concurrent placebo control group does not exist after an average 18 weeks of therapy.

bought for 12 weeks only!

Certainly, longer follow-up of all the patients on the uncontrolled extension trial, and a more thorough analysis of the data which have already been collected, will be necessary to draw additional conclusions.

alternative explanation for mortality:

The T (AZT) vs. 19 (PCB) is fraudulent!

It is incompatible with Phase I results, and also was incompatible with uncontrolled trial results!

(16) The major concerns which still remain regarding the chronic use of zidovudine in HIV-infected individuals include the following:

a) There is uncertainty about how long the beneficial effects will last. In the seriously ill patients studied in the controlled trial, zidovudine therapy conferred significant benefit both in terms of reduced mortality and incidence of OI's for the duration of the placebo-controlled study. After 18 weeks of therapy, (the average length of treatment at the time the placebo arm was discontinued in September 1986), it appears that the incidence of OI's in the zidovudine group increased to at least that observed in the first month of treatment. Only one zidovudine recipient died during the placebo-controlled portion of the trial, and eleven more have died since (ten AIDS and one ARC at entry). While 11 deaths in 60 AIDS/post-PCP patients (14%) (including two "suicides" and one death in a patient who was on zidovudine for only one week) over an average 35-30 week period is considerably lower than the generally quoted median life expectancy of 35-40 weeks in newly diagnosed AIDS patients following a first episode of PCP, it is possible that the number of deaths in this cohort may increase rapidly over the next 3-6 months, as the risk of developing an OI increased rather substantially after 18 weeks of therapy.

b) There is concern regarding the administration of zidovudine to less ill, less immunocompromised HIV-infected patients in whom the risk:benefit ratio of prolonged therapy is unknown. The cumulative toxicity of zidovudine, particularly at doses of 200-250 mg every four hours over long periods of time, may predispose these patients to more complications of HIV disease than inhibition of viral replication prevents. On the other hand, less ill patients with more intact immune systems may tolerate the drug better even over the long term (or possibly achieve a comparable antiviral effect with lower doses of zidovudine) and thereby sustain a net beneficial effect.

c) The optimum dose of zidovudine is unclear at this time. While it has been demonstrated that 250 mg every 4 hours exerted a beneficial effect in the placebo-controlled trial, many patients required dose reductions and/or temporary discontinuations, and it is unknown whether a lower dose or a different schedule of administration would be equally efficacious with less toxicity. On the other hand, a higher dose, if tolerated, might confer greater benefit, particularly to patients with HIV associated neurologic disease. Finally, the optimum dose may be different at different stages of disease.

It is also unclear whether zidovudine would be better administered at a dose which varies with body weight, rather than at a single dose regardless of weight.

d) The optimal approach to managing zidovudine-associated hematologic toxicity is unclear at the present time. In the controlled trial, red blood cell (RBC) toxicity (in the absence of neutropenia) was managed in several different ways: 1) with transfusions alone while continuing the full dose of zidovudine, 2) with temporary discontinuation of therapy with or without transfusions, as needed, or 3) with dose reduction with or without transfusions, as needed. The last alternative appears to be ineffective in that all patients managed in this way required eventual drug discontinuation for anemia despite the dose reduction.

It is also unclear how neutropenia is best managed in that 1) neutropenia often occurred in combination with anemia, 2) recovery of neutrophil counts in patients with neutropenia occurred in a few patients without change in dosage and in some with only a dose reduction, 3) baseline neutrophil counts are often low in patients with AIDS and advanced ARC. This fact, along with the known normal daily fluctuations in neutrophil counts in people generally, combine to make it difficult to determine in the individual patient whether or not a low count is related to zidovudine therapy, or alternatively, whether a particular dose modification (reduction or temporary discontinuation) is responsible for a subsequent rise in the granulocyte count.

A controlled study in which the alternative approaches to managing both RBC and WBC toxicities are compared in a randomized fashion is needed.

e) A major concern regarding widespread use of zidovudine is the potential for increased toxicity when administered with other drugs, particularly those that are myelotoxic, nephrotoxic, cytotoxic, glucuronidated, or have a similar mechanism of action (i.e. interference with replication of DNA). The therapeutic ratio of zidovudine in patients for whom it had been shown to be of benefit is not high, and additional toxicity caused by the co-administration of another agent may result in reduced efficacy.

f) The lack of data regarding the safety and efficacy of zidovudine in pediatric patients is also of concern. While limited Phase I pharmacokinetic and tolerance studies have begun in children, there is very little information as yet. Infants younger than two years have not been studied at all, and the toxicity and metabolism of zidovudine in young infants with immature hepatic and renal function may be substantially different than in adults or older children. Well designed studies addressing these issues are needed.

Recommendations

1. Zidovudine (Retrovir) 100 mg capsules should be approved for use in the management of patients with symptomatic HIV infection who have an absolute T-helper cell count of less than 200/mm^3 in the peripheral blood.

2. This recommendation is based primarily on the data submitted on December 2, 1986 in the original NDA summarized in the preceding medical review. Although there is only one adequate and well-controlled trial to support the approval, the significance of the results are so great that they can only be attributed to a beneficial effect of the drug. However, important follow-up data on the patients continuing in the open-label extension trial of zidovudine has been requested from the sponsor. Desk copies of much of this data have already been supplied to this medical officer, reviewed in a preliminary fashion, and tentative conclusions discussed under Item 15 in the preceding section of this review. These follow-up data provide important supportive evidence for the efficacy of zidovudine in that 1) after nine months of treatment, mortality in the original zidovudine group is still less than it was in the placebo group after 4 1/2 months of treatment, and 2) a more advanced group of patients (i.e. the original placebo group at the conclusion of the controlled trial) appears to have experienced a reduction in the risk of death and acquisition of OI's after beginning zidovudine therapy. These data will be analysed in more detail after they are officially submitted to the NDA.

3. The Burroughs Wellcome Company and others sponsoring clinical trials of zidovudine in HIV-infected individuals are encouraged to conduct well designed studies addressing important questions which still exist regarding the optimal use of this drug, particularly in less ill patients in whom it has not yet been studied, as discussed in the preceding section of this review.

if valid

Ellen C. Cooper, M.D.

Ellen C. Cooper, M.D., M.P.H.

cc:
Orig NDA 19-655 3/12/87
HFN-340 Original was initialed 3/9/87. E.T.
HFN-815
HFN-815/CSO/JKnight
HFN-815/MO/ECCooper:bam:3/5/87:1882m & 2082m
GRs on leave

Pharacology data Review (192

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA #1

NDA 19-655 (Original Submission, dated 12/2/86
and Amendments dated 12/16/86 & 12/19/86)

Date Review Completed: 12/29/86

Applicant: Burroughs Wellcome Co.

Drug: Retrovir™ Capsules, 100 & 250 mg

Generic Name: Zidovudine

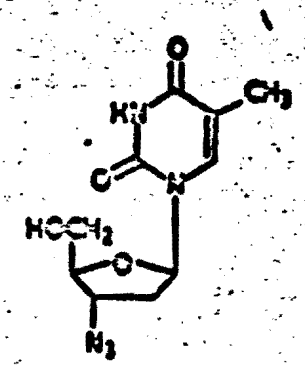
Other Names: AZT; Azidothymidine

Code Designation: BW A509U

Category: Antiviral (reverse transcriptase inhibitor)

Chemical Name: 3'-azido-3'-deoxythymidine

Chemical Structure



Composition: 100 or 250 mg AZT per capsule + excipients

Proposed Clinical Indication (labeling): "Management of certain patients with serious manifestations of infections caused by the human immunodeficiency virus (HIV)." Apparently, this includes ARC as well as AIDS patients.
Proposed Dosage: 200-250 mg q 4 h (1200-1500 mg daily). [Note: The table in the dosage & administration section (p. 2-00013) may be misleading because the dose for a 60-80 kg could be interpreted as two 100 mg capsules and one 250 mg capsule (rather than one or the other). Also, the table lists the dose for a 80-100 kg patient as three 100 mg capsules/dose, i.e. 300 mg.]

PRECLINICAL DATA

PREVIOUSLY REVIEWED

This application contains the following reports which have been previously submitted and reviewed in connection with

(Note: In type of submission column, O = Original Submission, A = Amendment)

NDA Ref. No.	Previous Submission No.	Type	Date	
TOXICOLOGY REPORTS				
Acute Toxicity				
1. "An Acute Intravenous Toxicity Study in the Mouse with BW 0509U81"				O
2. "An Acute Intravenous Toxicity Study in the Rat with BW 0509U81"				•
Subacute/Subchronic Toxicity				
3. "A Two-week Oral Dose Range-finding Study of BW 0509U81 in Charles River CD Rats"				O
4. "A Three-month Oral Toxicity Study with BW 0509U81 in Charles River CD Rats"				A
5. "A One-month Intravenous Toxicity Study in Charles River CD Rats with BW 0509U81"				O
6. "A Two-week Oral Dose Range-finding Study of BW 0509U81 in Beagle Dogs"				O
7. "A Two-week Intravenous Toxicity Study in Beagle Dogs with BW 0509U81"				O
8. "A Two-week Oral Dose Range-finding Study of BW 0509U81 in Cynomolgus Monkeys"				A
9. "A Three-month Oral Toxicity Study of BW 0509U81 in Cynomolgus Monkeys"				A
Reproduction-Teratology				
11. "A Dose Range-finding Study of BW 0509U81 in Pregnant CD Rats"				A
12. "A Teratology Study in Rats Given BW 0509U81 by Gavage"				A
13. "A Dose Range-finding Study of BW 0509U81 in NZW Rabbits"				A
Mutagenicity				
14. "Salmonella/Mammalian-Microbial Mutagenicity Studies in BW 0509U81"				A

15. "Mutagenicity Study with BW 0509U81 in L5178Y/TK +/- Mouse Lymphoma Cells With and Without Exogenous Mammalian Metabolism"

16. "An In Vitro Cytogenetic Study in Cultured Human Lymphocytes BW 0509U81"

ADME REPORTS

2. Good SS: The disposition of BW 509U in the rat.

3. deMiranda P, Burnette T: Tissue distribution and metabolic disposition of azidothymidine (AZT, BW A509U) in rats.

4. Krasny HC: Protein binding of BW A509U in human, dog and rat plasma.

6. Krasny HC: The Pharmacokinetics of BW A509U in the dog following IV bolus administration of the drug.

7. Krasny HC: Preliminary report on pharmacokinetics and metabolism of BW A509U in dogs.

9. deMiranda P et al: Pharmacokinetics and metabolism of azidothymidine (AZT) in the cynomolgus monkey.

13. Good SS, deMiranda P: Metabolic fate of BW A509U in humans and various species.

14. Same study as #13, resubmitted at a later time.

15. Apps EP, Parsons DW: A qualitative whole-body autoradiographic study of the distribution of radioactivity in male albino mice following the intravenous administration of (^{3}H)-509U81 at 15 mg/kg^{-1}.

16. Burnette TC: Three month oral toxicity study with BW 0509U81 in Charles River CD rats (Tox 374): Plasma levels of BW 0509U81 on dose day 2.

17. Burnette TC: Three month oral toxicity study with BW 0509U81 in Charles River CD rats (Tox 374): Plasma levels of BW 0509U81 on dose day 91.

19. Burnette TC, deMiranda P: A 13-week oral toxicity study of BW 599U81 in Cynomolgus monkeys (Tox 383): Plasma levels of BW 509U81 and its metabolite, GAZT, on dose day 2.

20. Burnette TC, deMiranda P: A 13-week oral toxicity study of BW 509U81 in Cynomolgus monkeys (Tox 330): Plasma levels of BW 509U81 and its metabolite, GAZT, on dose day 87.

22. Burnette TC: Teratology study in rats given BW 509U81 by gavage (Tox 307): Measurements of evidence of absorption.

NOT PREVIOUSLY REVIEWED

The following reports have not previously been reviewed.

1. AZT in the Cat

Blood samples collected at various intervals after a 5 mpk SC dose of BW 509U81 in one cat showed highest plasma levels (4.2-4.3 mcg/ml) at 15-30 minutes and background level at 6 hrs; half-life was 0.8 hr. The 0-24 hr urine contained only 23% of the dose as unchanged drug. No information regarding metabolites was obtained from this experiment.

In the same cat, a dose of 5 mpk by gavage produced a plasma peak of 2 mcg/ml at 0.5-1.0 hr and background level at 6 hrs; half-life was 0.9 hr. Urinary recovery was again only 23% of the administered dose and no there was no information about metabolites.

Two kittens given 7.5 mpk SC had plasma levels of approx. 5 mcg/ml at 40 min. and 1.5 mcg/ml at 5 hrs.

2. Blood Levels from 6-Month Oral Toxicity Study in Rats [Ongoing study # 1, below]

Mean plasma levels on day 2 of this study were 4, 18 & 83 mcg/ml for animals (3/sex/dose) given 50, 150 or 500 mpk, respectively.

3. Cell Transformation Assay

This BALB/c-3T3 neoplastic transformation assay was performed according to standard operating procedure. Conc'ns of AZT as low as 0.1 mcg/ml reduced the no. of cells in culture after a 3-day exposure. A stat. sig. increase in the no. of aberrant "foci" was noted at a conc'n of 0.5 mcg/ml. This behavior is characteristic of tumor cells and suggests that AZT may be a potential carcinogen. It appears to be at least as active as the positive control material, methylcholanthrene.

4. Cytogenetic Study in Rats [Culture & dosing done at BW; analyses performed ?

Groups of rats (4/sex/gp) were given single doses of 37.5, 75, 150 or 300 mpk AZT IV. Colchicine was given IP 2 hrs prior to sacrifice which was 6, 24 or 48 hrs after the AZT. Negative (saline) & positive (cyclophosphamide) controls were included. Immediately after sacrifice, bone

marrow cells were collected from both femurs and processed according to standard techniques for chromosome analysis. Other groups of animals received 0, 37.5, 75, 150 or 300 mpk IV and were sacrificed 5 min. or 4 hrs later for plasma drug conc'n determinations.

There was no increase in structural chromosome aberration frequency at any dose of AZT, relative to controls. Similarly, there was no increase in the percentage of cells with other than 42 chromosomes.

Plasma levels 5 min. after the IV dose were 100, 330, 640 & 1650 micromole AZT and 10, 17, 20 & 30 micromole GAZT. Four hrs later, the drug had virtually disappeared from the plasma.

5. Blood Levels from Teratology Study in Rabbits [Study completed, but not yet reported; # 3 below]

Plasma levels on the last day of treatment (50, 150, 500 mpk/day orally on days 6-18 of gestation) were too dissimilar to average. However, in individual animals, the level of BW 0509U81 was 2-3x greater than the GAZT level. Fetal tissue levels of BW 0509U81 were approx. 1/3 the maternal plasma level.

INCOMPLETE

The following studies are currently underway (1-3) or planned (Nos. 4-11) as per our meeting with the applicant on 10/6/86.

1. Six-month Oral Toxicity in Rats: Doses of 0, 50, 100 or 500 mpk/day were given by gavage in 2 equal divided doses 6 hrs apart. Preliminary results showed slight to mild decrease in RBC at the HD (day 180). Terminal sacrifice was scheduled for 10/20-24/86.

2. Six-month Oral Toxicity Study in Monkeys: Doses of 0, 35, 100 or 300 mpk were given daily as in the rat study. Preliminary results indicated mild to moderate anemia in the MD & HD animals (day 60). Termination was scheduled for 12/1-2/86.

3. Oral (Segment II) Teratology Study in Rabbits: The animals were given 0, 50, 150 or 500 mpk/day by gavage as above, on gestation days 6-18. No treatment-related changes were seen in the fetuses. The report of this study is in the final stages of preparation.

4,5. Oral Carcinogenicity Studies in Rats & Mice: Dose levels and start date will be chosen after completion of 30-day dose range-finding studies using once a day rather than divided dose administration.

6. One-year Oral Toxicity Study in Rats: Doses of 0, 50, 150 or 450 mpk/day by gavage in 2 divided doses 6 hrs apart. The tentative study start date is in February, 1987.

7. One-year Oral Toxicity Study in Monkeys: Doses of 0, 35, 100 or 300 mpk/day administered as in the 1-year rat study; also to start in February, 1987.

8. Oral Neonatal Toxicity Study in Rats: Eight-day old animals are to be treated for 42 days; doses will be based on results of a dose range-finding study. The study is to begin in March, 1987.

9. Oral Segment I (Reproduction-Fertility) Study in Rats: Doses of 0, 50, 150 or 450 mg/kg in divided doses 6 hrs apart will be given by gavage to males for 70 + days prior to mating, and to females for 14 days prior to and through mating, during gestation, delivery, until the 20th day of lactation. Starting date was set for 1/6/87.

10. Repeat Oral Segment II (Teratology) Study in Rabbits: Because of poor pregnancy rates & deaths of does from intubation errors, only a few litters were available in the first study (#3, above). Three doses (to be determined) will be given 2x/day by gavage on days 6-18 of gestation. Study to start in March, 1987.

11. Oral Segment III (Peri- & Postnatal) Study in Rats: Doses of 0, 50, 150 & 450 mg/kg by gavage as described above to pregnant rats from day 17 of gestation thru delivery until day 21 of lactation. Starting date: March, 1987.

PROPOSED LABELING

"WARNINGS"

Since the average duration of treatment in the only double-blinded placebo-controlled study of AZT attempted was only 4.5 months, the label should state that the full safety & efficacy profile has not been completely defined "for greater than 16-week use" rather than "for long-term usage."

"PRECAUTIONS"

1. It is presumptive to include data from the rabbit study in the pregnancy section, since it has not yet been submitted. The only reproduction study submitted thus far is rat teratology. Therefore, the words "and rabbits" should be removed from the labeling.

2. In the in vitro cytogenetic study using human lymphocytes data were equivocal (negative control values similar to positive control). Therefore, the applicant's statement that structural, but not numerical, abnormalities were induced is not scientifically accurate.

3. The sentence: "The significance of these in vitro results is not known." is not accurate. A test chemical which induces a positive response in the cell transformation assay is presumed to be a potential carcinogen.

4. Results from the the in vivo cytogenetic studies are cited, but the data have not yet been submitted.

5. Tests to detect the potential to induce tumors have not even been "started"; they are not "completed", as stated in this section.

OVERDOSAGE

Although there was no "mortality" in monkeys given 300 mg/kg/day or rats given 500 mg/kg/day, there was anemia. This statement should be modified, not only to ensure accuracy of information, but because of its correlation with anemia noted in patients.

SUMMARY, COMMENTS & RECOMMENDATIONS

1. AZT (zidovudine) is a thymidine analog which has been reported to inhibit replication of AIDS virus (HIV) in vitro. Apparently, it is phosphorylated intracellularly and inhibition of HIV reverse transcriptase by the triphosphate derivative is the major mechanism for its antiviral activity. AZT has shown activity (in vitro) against several other retroviruses (e.g., ED virus, HTLV-I) as well. Antimicrobial activity against certain bacterial & protozoal pathogens has also been demonstrated.

2. The proposed labeling recommends treatment of AIDS (and ARC?) patients with oral doses of 200-300 mg q 4 h for an unlimited period.

3. Preclinical toxicity data submitted in support of the application include results of studies in rats, dogs and cynomolgus monkeys. FDA guidelines would have prescribed more extensive preclinical testing than that reported thus far. However, the urgency for developing an anti-AIDS drug has been so great that clinical testing has preceded the usual/customary preclinical testing. For example, while data from a 6-month clinical study are available, results of the supporting 6-month preclinical toxicity studies have not yet been submitted. Also, the applicant has a protocol for a 104-week clinical study, whereas chronic (52-week) preclinical toxicity studies are not scheduled to start before January-February of this year.

4. Rats given 500 mg/kg/day orally in 2 divided doses (6 hrs apart for) 3 mos. had decreased Hgb & RBC. However, animals given 250 or 500 mg/kg/day orally as a single daily dose for 2 wks had hepatocellular vacuolation and/or necrosis and nephritis.

   Dogs appear to be especially susceptible. Profound toxicity was noted in beagles given doses of 125-500 mg/kg/day for 2 wks, including moderate-marked leukopenia & anemia and hypocellularity of the bone marrow.

   Monkeys receiving 34, 100 or 300 mg/kg/day orally for 13 wks showed a dose-related progressive decrease in RBC throughout the study and a drop in Hgb & Hct between study day 1 & 21. At the HD level, MCC was also decreased.

   Anemia has been encountered in patients given 1500 mg/day (i.e., about 25 mg/kg/day) for 6 mos. More serious side effects have also not been noted, e.g. granulocytopenia.

   Thus, although the dose varied, anemia was noted in all species (including man) in which the drug has been tested.

5. Although AZT was negative in the Ames Test, it was found weakly mutagenic

in vitro in the mouse lymphoma cell system. Dose-related chromosome damage was observed in an in vitro cytogenetic assay using human lymphocytes.

6. In an in vitro neoplastic transformation assay (Balb/C 3T3 cells in culture), AZT showed considerable activity at concentrations as low as 0.1 mcg/ml. Long-term in vitro carcinogenicity studies are planned but have not yet been initiated.

7. Similarly, although the drug had no teratogenic effect in the segment II rat teratology study, the planned segment I & III studies in rats and repeat segment II study in rabbits have to be done before the effect of AZT on reproductive function and the safety of its use during pregnancy can be predicted.

8. For comments on proposed labeling, see above.

9. ADME data were obtained in 7 animal species. Although each study was extremely limited in terms of no. of animals used (i.e. as few as one), the pattern of metabolism & excretion is fairly clear. The major excretory route is via the urine. In most species, nearly all the drug appears as the free drug (AZT). The cynomolgus monkey, however, excretes it mostly as the glucuronide conjugate (GAZT), the same excretory pattern which is identified for humans. These data would suggest that presence of more drug in the free form may account for the greater toxicity in dogs & rats (vs. the conjugate, as in monkeys & humans).

10. In conclusion, the full preclinical toxicological profile is far from complete with 6-month data available, but not yet submitted, one-year studies to begin shortly, etc. The available data are insufficient to support NDA approval. Also, the application should not be approved at this time because, with its antimicrobial spectrum, AZT might be perceived as also potentially efficacious, and be prescribed for, diseases other than AIDS. Inasmuch as the applicant has an active treatment IND, the drug would still be available for AIDS patients, even if this NDA were not approved at this time.

Harvey I. Chernov, Ph.D.

Supervisor's Comment: If maintenance or expansion of the IND treatment program will result in an overwhelming economic burden for the applicant, perhaps temporary subsidy from public funds should be considered.

cc: Orig. IND
HFN-815
HFN-815/HD
CSO
HFN-840
HFN-815/HIChernov/sac/1/13/87
R/d init.b :JHDavitt
C4O1p

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 19-835 (Amendment, dated 2/10/87)

DATE REVIEW COMPLETED: 2/12/87

SPONSOR: Burroughs Wellcome Co.
Research Triangle Park, NC

DRUG: Retrovir^{R} (zidovudine); BW A 509 U; AZT

CATEGORY: Anti-Viral

CLINICAL INDICATION: AIDS

CHEMICAL NAME: 3'-Azido-3'-deoxythymidine

PRECLINICAL STUDY

Six-Month Oral Toxicity Study: [Performed by Sponsor; sperm evaluation done by

Methods: Charles River CD rats, 12/sex/dose group, were given AZT by gavage at 30, 100 or 300 mpk/day in 2 equal portions 6 hrs apart. Control group received distilled water.

Results:

Mortality: 2-3 rats/group (5 in HD gp) - dosing accident or undetermined cause

Clinical Signs: Salivation post-dose all HD M & F, wks 1-26; also stains on bodies of some HD rats

Body wt; Food intake: HD M rats gained more wt than controls; all other gps had growth curves similar to controls. Drug had no effect on food intake.

Hematology; Clinical Chemistry: HCT & HGB decreased slightly in HD F only; RBC decreased & MCV increased in HD M & F. Values returned to normal during post-dose recovery period. Drug had no effect on WBC. Blood glucose was increased in HD M & F; SGOT was elevated in F at all doses.

Ophthalmology: No toxicity was noted.

Drug Plasma Conc'ns: One-half hr after the 2nd daily dose, mean levels of AZT were 4.2, 17.6 & 83.2 on day 2 & 9.7, 34.4 & 142 mcg/ml on day 177 for rats given 30, 100 & 300 mpk, respectively.

Semen Evaluation (Postmortem): No drug effect on parameters monitored (sperm motility, epididymal sperm density, incidence of abnormal sperm).

Organ Wt: At day 57 post-dose (but also at study day -1), there was increased liver wt (abs. & rel.) in HD F.

Gross & histopathology: In neither the rats found dead nor those at terminal sacrifice were there any remarkable drug-related findings.

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NDA 19-515 Page 2

COMMENTS

Contrary to the applicant's statement (p. 2 of the report), signs of anemia were also noted at 500 mpk in the 3-month oral toxicity study in rats. However, the current data demonstrate that administration of the drug over a longer period does not result in a more severe anemia. Furthermore, the condition is reversible shortly after cessation of drug.

Rather than being "abnormally low" (report, P. 9) the mean drug plasma conc'n in HD rats at day 2 in this study was 63 ng/ml (142 ng/ml on day 177) and 100-130 on days 2 & 91 in the earlier (3-mo.) study. It would appear that more can be said for animal-animal variation than for drug accumulation.

Other than the anemia noted above, AZT at 500 mpk/day (ca. 20x proposed clinical dosage) for 6 mos. produced virtually no toxicity in rats.

Harvey I. Chernov, Ph.D.

cc: Orig. NDA
HFN-815
HFN-815/MO
HFN-340
HFN-815/hIChernov/smc/3/3/87
R/d init.by:JLDavitt
084up

203

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 19-655 (Amendment, dated 1/13/87)

Date Review Completed: 1/21/87

Applicant: Burroughs Wellcome Co.

Drug: Retrovir^{R} (zidovucine; "AZT")

Category: Antiviral

Chemical Name: 3'-azido-3'-deoxythymidine

Clinical Indication: AIDS

Related INDs:

PRECLINICAL STUDY

Segment II Oral Teratology Study in Rabbits: Pregnant NZ white rabbits, 17/group (4/gp for drug plasma evaluation) were administered C (0.5% methylcellulose), 50, 150 or 500 mpk/day given as 2 equal portions by gavage, 6 hrs apart, on gestation days 6-18.

Mortality: None drug-related, but 12 due to dosing accidents (includes 2 controls & 6 HD) and one that aborted.

Clinical Signs: "Red material" caused by technical errors; also, labored breathing.

Body Wt; Food Intake: No significant effect.

Maternal Survival/Pregnancy Status: Only 6-8 dams/group with viable fetuses.

Mean Fetal Data: 50% fewer viable fetuses & implantation sites in the HD than in controls; early resorptions & post-implantation loss higher in LD & MD (but not HD) groups; no dead fetuses in any group; wts of fetuses in all gps were comparable.

Fetal Malformations/Variations: Increased no. of fused sternebrae in the LD only; no visceral findings; bent hyoid arches (LD) & sternebrae #5 and/or #6 unossified (MD).

SUMMARY

Doses of AZT as high as 500 mpk/day orally for 13 consecutive days to pregnant rabbits were not toxic to the dams. Similarly, any fetal effects noted appeared to be incidental rather than drug-related. However, because of the limited no. of litters available for examination, the applicant plans to repeat this study.

cc: Orig. NDA
HFN-815
HFN-815/MO
CSO
HFN-340
HFN-815/HIChernov/smc/2/3/87
R/d init.by:JMDavitt
OSE7p

Harvey I. Chernov, Ph.D.

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REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 19-655

APPLICANT: Burroughs-Wellcome Co.

DRUG: Retrovir (zidovudine; "AZT") Capsules

The initial pharm/tox review of this application (12/29/86) listed a number of animal studies either planned or underway at that time. The current status of those studies is as follows:

1. Six-month Oral Toxicity in Rats: Final report submitted 2/10/87 (reviewed 2/13/87).

2. Six-month Oral Toxicity Study in Monkeys: An unaudited draft report was hand-delivered to us on 1/15/87. It contains antemortem data and necropsy findings on the animals sacrificed at 6 months. (Principal finding seems to be dose-related anemia). Dr. Ayers (B-W) has informed us that we can expect to receive the final report on all but the recovery animals by next week.

3. Oral (Segment II) Teratology Study in Monkeys: Final report was submitted 1/13/87 (reviewed 1/21/87).

4,5. Oral Carcinogenicity Studies in Rats & Mice: Rat study was started on 1/21/87. Mouse study is scheduled to start on 4/7/87.

6. One-year Oral Toxicity Study in Rats: This study was started on 2/10/87.

7. One-year Oral Toxicity Study in Monkeys: This study was started on 3/4/87.

8. Oral Neonatal Toxicity Study in Rats: A dose-range finding study has been done, using doses as high as 750 mg/kg/day. Slight hematological changes were noted.

9. Oral Segment I (Reproduction-Fertility) Study in Rats: Animals are about ready to breed at this time.

10. Repeat Oral Segment II (Teratology) Study in Rabbits: Dr. Ayers (B-W) has informed us that this study will begin in April, using doses higher than in the previous study (i.e., 750-1000 mg/kg).

11. Oral Segment III (Peri- & Postnatal) Study in Rats: Not yet started (was scheduled for this month).

Attached is a compilation of summaries of all toxicity studies submitted thus far, extracted from previous pharmacology reviews of the NDA.

Harvey I. Chernov, Ph.D.

John M. Davitt, Supv. Pharm.

cc: Orig. NDA
HFN-815
HFN-815/Cooper
Knight
HFN-346
HFN-815/HIChernov/smc/3/6/87
R/d init.by:JMDavitt
0555p

606

ZIDOVUDINE (AZT) PRECLINICAL TOXICITY STUDIES

(207

Acute Toxicity

Proj. Rat. #'s: TTEP/85/C010 & TTEP/85/C009

Formulation Tested: DW in 0.9% saline

Dose Level, Route & Duration: 750 mpk; single dose; IV

Species & Sex: M & F CR CD-1 mice; M & F CR CD-1 rats

LD_{50}: Greater than 750 mpk for both species

Observations

Mice: 1/10 F died during dosing at 487 mpk (no clinical or pathological signs noted in this mouse). A majority of the mice showed dec'd activity & ptosis immediately after to 35 min. PD. Labored breathing was seen immediately after dosing in some mice, clonic convulsions 3 min. PD in 1 mouse. All mice appeared normal by 116 min. PD & during the 14-day PD period.

Rats: Labored breathing, dec'd activity & ptosis from 1-15 min. PD (signs lasted from 31-144 min. PD). Rats were normal throughout the 14-day PD period.

Two-week Toxicity - Dog

Proj. Pot. #: TREP/CS/C311

Formulation Tested: SW in 0.5% saline

Species, Sex & # Animals: M & F beagle dogs; 3/sex/dose level; 1/sex from each test (2) & controls held for 14-day PD recovery.

Dose Levels, Route & Duration: 21.5 (LD), 42.5 (MD) & 85 (HD) mg/kg and controls (0.5% saline); IV for 14 consec. days; total daily dose divided into 2 equal doses given 6 hrs apart.

Parameters Evaluated	Dose Days
clinical signs	daily
body wt, food intake	weekly
clinical chemistry	-4, -2, 6, 12, 14, +14
hematology	-4, 6, 14, +14
ophthalmic exam	-8, 14, +13
EKG	-14, -7, 5, 13, +12
scheduled sacrifice & organ wts	+1, +15
gross exam & histopathology	all dogs sac'd on schedule

Results

Clinical Signs: Emesis on one occasion in 1/3 LD F, 1/3 MD M & 1/3 HD F

Body Wt

- During treatment: slight dec. in MD M
- Recovery period: inc. at all dose levels

Food Intake: No drug-related changes during treatment or recovery.

Hematology (Mean Values)

End of 2-Week Treatment

	Low Dose		Mid Dose		High Dose	
Decreased	M	F	M	F	M	F
RBC; slight-mod.	X	X	X		X	X
Hgb; slight	X	X	X		X	X
HCT; slight	X	X	X		X	
MCV; mod.*	X		X	X	X	X
% segmented neutrophils; slight	X			X	X	X
% nonsegmented neutrophils; slight	X		X		X	
% monocytes; mod.*	X	X	X	X	X	X
abs. seg. neutrophils; sev.	X		X	X	X	X
abs. nonseg. neutrophils; sev.	X		X		X	X
abs. lymphocytes; sev.	X		X	X	X	X
abs. monocytes; sev.*	X	X	X	X	X	X
abs. basophils; slight-sev.*	X		X		X	
platelets; mod.				X	X	X
eosinophils; slight		X			X	
abs. eosinophils; mod.-sev.		X		X		X
Increased						
% eosinophils; slight-mod.	X		X		X	
abs. eosinophils; moderate-sev.	X		X		X	
% RDW; slight	X	X	X	X	X	
% lymphocytes; slight-mod.*		X		X		X

Organ Wts

End of 2-week Treatment

	Abs.	Rel.	Low Dose M	Low Dose F	Mid Dose M	Mid Dose F	High Dose M	High Dose F
Increased								
Adrenal	X	X		X		X		X
Thyroid	X	X		X		X	X	X
Brain	X	X	X	X[e]		X[e]	X	X[e]
Kidney	X	X	X	X[c]		X[c]	X	X[c]
Liver	X	X	X	X	X	X	X	X
Testes	X	X					X	
Decreased								
Adrenal	X	X	X[a]		X[a]		X[a]	
Pituitary	X	X	X		X	X	X	X
Brain	X	X[b]			X		X	
Kidney	X	X		X[d]	X	X[d]		X[d]
Testes	X	X	X		X			

End of 14-day Recovery

	Abs.	Rel.	Low Dose M	Low Dose F	Mid Dose M	Mid Dose F	High Dose M	High Dose F
Increased								
Adrenal	X	X		X		X		X
Pituitary		X		X				
Brain	X	X				X		X
Kidney	X	X	X		X			
Liver	X[f]	X[g]	X	X	X	X	X	X
Testes	X	X	X		X			
Decreased								
Adrenal	X	X	X		X		X	
Pituitary	X	X	X	X		X	X	X[a]
Brain	X	X[h]	X	X	X		X	X
Kidney	X	X				X	X	X
Liver	X					X		
		X					X	
Testes	X	X					X	

a = dose-related; b = dec'd at HD only; c = inc. in rel. wts only; d = dec. in abs. wts only; e = dose-related for rel. wts; f = inc. in LD & HD F only; g = inc. in LD & MD M only; h = dec. in abs. wts only

Gross Pathology

- End of 2-week Treatment: Thymus: Diffuse hemorrhage in 1/2 control F, 1/2 LD F & 1/2 HD M. According to the sponsor, hemorrhage was probably "due to jugular blood withdrawal procedure."

- End of 14-day Recovery: Drug-treated gps were similar to controls.

Histopathology

End of 2-week Treatment (2/sex/group)

	Control M	Control F	Low Dose M	Low Dose F	Mid Dose M	Mid Dose F	High Dose M	High Dose F
Heart: paravasculitis							1	
Liver: hemosiderosis, Kupf. cells					1			
Spleen:	2				1		1	
extramed. hematopoiesis					1			
Cervical Lymph Node: congestion				1		1		
Mesenteric Lymph Node: congestion	1				1			1
Thymus: involution, hemorrhage	2	1	1	2	2	2	2	1
perithymic		1		1			1	
Stomach: gastritis granulomatous			1					
Skin: dermatitis w/focal derm. squamous metaplasia		1						
Skeletal Muscle: myositis			1					
Adrenal: cortical vacuolation								1
Pituitary: microcyst, pars anter.	1	2						
Injection Site: perivasculitis	2	2	1	2		2	1	2
hemorrhage	2	2	2	2	2	1	2	2
dermatitis								1

End of 14-day Recovery (1/sex/group)

	Control M	Control F	Low Dose M	Low Dose F	Mid Dose M	Mid Dose F	High Dose M	High Dose F
Spleen: hemosiderosis		X		X				
Thymus: involution	X	X	X			X		X
Pituitary: microcyst pars anter.	X		X	X	X			
Injection Site: perivasculitis	X					X		
hemorrhage	X	X	X	X	X	X	X	X

Ophthalmology: The sponsor concluded that "for the dosage & duration studied, Bx demonstrated no ocular toxicity in beagle dogs."

EKG: Ten lead (I, II, III, aVR, aVL, aVF, rV_2, V_2, V_4 & V_{10}) EKGs taken 2x pretest, on days 1, 7, 5 & 13 of treatment, and on recovery day 12, on 2 dogs/dose gp, were negative for drug-induced activity.

(ΣLI)

One-month IV Toxicity in Rats

Prel. Rpt. #: TTEP/OS-0023

Formulation Tested: BW in 0.9% saline

Species, Sex & # Animals: M & F CD rats; 12/sex/dose level (at termination of study, 6/sex/dose were sacrificed & 4/sex/dose held for 2-week PD drug-free recovery); another group of 6/sex/dose were sacrificed on day 13 for hematology & clinical chemistry.

Parameters Evaluated	Dose Days
clinical signs	daily
body wt; feed intake	weekly
clinical chemistry; hematology	-8, -7, 13, +1, +18
ophthalmic exam	-10, 26, +14
schedules sacrifice; organ wts	+1, +18
gross exam	all rats dead/killed at sched. sac.
histopathology	control & HD, sac. at end of dosing; HD rats dying during dosing

Dose Levels, Route & Duration: 0 (Control), 38 (LD), 75 (MD) & 150 (HD) mg/kg/day; IV bolus for 4 weeks; controls received 0.9% saline

Results

Mortality: 1/12 HD F died on dose day 6 (no cause for death given). Histopath. report noted congestion of kidney, liver, lung, cervical lymph node & thymus and mild perivasc. hemorrhage at the injection site. 1/6 LD F in the clinical path. gp died on day 7 (sponsor states that death was due to accidental admin. of air during dosing).

Body Wt & Food Intake: No drug-related changes.

Hematology (Mean Values)

End of 5-Week Treatment	Low Dose M	Low Dose F	Mid Dose M	Mid Dose F	High Dose M	High Dose F
Decreased						
RBC; slight	X				X	
% seg. neutrophils; slight-mod.	X		X		X	
abs. seg. neutrophils; mod.-sev.	X		X		X	
platelets; mod.-sig.		X	X	X	X	X
% lymphocytes; slight				X		X
% monocytes; slight		X		X		X
% eosinophils; slight		X		X		X
abs. lymphocytes; sig.		X				
abs. monocytes; mod.-sig.		X		X		X
abs. eosinophils; slight-mod.		X				X
Increased						
MCV; slight	X		X		X	
MCH; slight	X		X		X	
WBC; slight-mod.	X		X	X	X	X
% lymphocytes; slight-mod.	X		X		X	
% monocytes; slight	X		X		X	
% eosinophils; slight	X		X		X	
abs. lymphocytes; sig.	X		X	X	X	X
abs. monocytes; mod.-sig.	X		X		X	
abs. eosinophils; mod.-sig.	X		X	X	X	

	Low Dose		Mid Dose		High Dose	
	M	F	M	F	M	F
End of 14-day Post-dose Recovery						
Decreased						
RBC; slight		X	X		X	X
Hgb; slight		X	X		X	X
HCT; slight			X		X	
MCV; slight	X		X	X	X	
% seg. neutrophils; slight-sev.	X		X	X	X	
% nonsegmented neutrophils; slight	X		X		X	
abs. seg. neutrophils; sev.	X		X		X	
abs. nonseg. neutrophils; sev.	X		X		X	
abs. lymphocytes; mod.-sev.		X		X		X
abs. monocytes; mod.-sev.		X		X	X	X
Increased						
% lymphocytes - sev.			X		X	
% eosinophils; mod.-sev.	X		X		X	
abs. lymphocytes; mod.-sev.			X		X	
abs. eosinophils; mod.-sev.	X	X	X	X	X	X
abs. basophils; sev.					X	
platelets; mod.-sev.		X			X	X
% RDW; slight-mod.		X	X	X	X	X
eosinophils; slight-mod.		X		X		X
abs. seg. neutrophils - mod.						X
abs. nonseg. neutrophils		X				X
Clinical Chemistry						
Increased						
Total bilirubin; slight-sev.	X		X		X	
Glucose; slight-mod.	X		X		X	
Hemolysis; slight-mod.	X	X		X	X	X
BUN; slight		X		X		X
Creatinine; slight						X
Decreased						
Potassium; slight		X				X
% ICG; slight-mod.		X		X		X
End of 14-day Recovery						
Increased						
Bilirubin; slight					X	X
Glucose; slight-sev.	X		X		X	X
BUN; mod.						X
Creatinine; mod.						X
Decreased						
% ICG; slight-mod.		X		X		X

End of 17-Day Recovery	Low Dose M	Low Dose F	Mid Dose M	Mid Dose F	High Dose M	High Dose F
Decreased						
RBC; slight	X	X	X	X	X	X
% seg. neutrophils; slight-mod.	X	X	X	X	X	X
% monocytes; slight-sig.	X	X	X	X	X	X
abs. seg. neutrophils; sev.	X	X	X		X	X
abs. lymphocytes; sig.			X			
abs. monocytes; mod.-sig.	X	X	X	X	X	X
abs. eosinophils; slight-mod.		X		X	X	X
platelets; mod.-sig.	X	X	X	X	X	X
WBC; mod.			X			
% eosinophils; slight		X		X		X
Increased						
WBC; slight	X	X		X	X	X
% lymphocytes; slight-mod.	X	X	X	X	X	X
abs. lymphocytes; sig.	X	X		X	X	X
abs. eosinophils; sig.	X		X			
abs. seg. neutrophils; sig.				X		
Treatment Day 13						
Decreased						
RBC; slight	X	X	X	X	X	
% seg. neutrophils; slight-mod.	X	X	X		X	
abs. seg. neutrophils; sig.	X	X	X		X	X
abs. lymphocytes; mod.-sig.		X	X	X	X	
% monocytes; slight						X
platelets; slight-mod.			X	X	X	
% lymphocytes; slight		X		X		X
Increased						
% lymphocytes; slight	X		X		X	
% monocytes; slight	X	X	X	X	X	
% eosinophils; sig.	X	X	X	X	X	X
abs. lymphocytes; mod.-sig.	X					X
abs. monocytes; slight-sig.	X	X	X	X	X	X
platelets; slight-mod.	X	X				X
WBC; slight						X
% seg. neutrophils; slight				X		X
abs. seg. neutrophils; mod.				X		
abs. eosinophils; mod.-sig.	X	X	X	X	X	X
Clinical Chemistry						
End of 4-week Treatment						
Increased						
BUN; slight			X		X	
glucose; slight-mod.	X	X	X		X	X
SGOT; mod.					X	
hemolysis			X	X	X	X
Decreased						
glucose; slight				X		

End of 12-Day Recovery	Low Dose M	Low Dose F	Mid Dose M	Mid Dose F	High Dose M	High Dose F
Increased						
Glucose; slight-mod.	X	X	X		X	
Potassium; slight						X
BUN; mod.						
Decreased						X
Glucose; slight						
Potassium; slight	X	X		X	X	X
Treatment Day 13						
Increased						
Total bilirubin		X		X	X	X
glucose; slight-mod.	X		X	X	X	X
Hemolysis	X	X		X		X
Decreased						
Potassium; slight					X	

Ophthalmology: 1/12 HD M had a nuclear cataract & 1/12 HD F had an anterior cataract.

Organ Wts

End of 4-Week Treatment	Abs.	Rel.	Low Dose M	Low Dose F	Mid Dose M	Mid Dose F	High Dose M	High Dose F
Increased								
Adrenal	X	X	X	X	X	X	X	X
Pituitary	X	X	X		X		X	
Liver	X	X	X[m]		X[m]		X	
Decreased								
Pituitary	X	X		X		X		X
Thyroid	X	X	X			X	X	X
Brain	X	X	X[j]	X	X[j]	X[k]	X	X
Kidney	X	X	X	X	X	X	X	X[n]
Liver	X	X		X		X		X
Testes	X	X					X	
End of 14-Day Recovery								
Increased								
Adrenal	X	X	X	X	X	X	X	X[i]
Brain	X	X		X[j]		X		X
Liver	X	X	X		X		X	
Decreased								
Pituitary	X	X		X[j]		X		X
Thyroid	X	X		X		X		X
Kidney	X			X		X[k]		X
Testes	X		X		X		X[k]	

i = inc. in abs. wt only; rel. wt same as controls
j = dec. in abs. wt only; rel. wt same as controls
k = dec. in abs. wt only; rel. wt inc'd
l = inc. in abs. wt only; rel. wt dec'd
m = dec. in rel. wt only; abs. wt inc'd
n = inc. in rel. wt only; abs. wt dec'd

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Two-week Oral Dose-range-finding Study in Rats

Proj. Rpt. #: TTOR/84/007

Formulation Tested: BW; vehicle not specified.

Species, Sex & # Animals: Charles River CD rats, M & F; 5/sex/dose level

Dose Levels, Route & Duration: 0, 60, 125, 250 & 500 mpk/day, orally by gavage for 14 consec. days

Parameters Evaluated: clinical signs (daily), body wts (weekly), liver & kidney wts, gross & histopath. (end of sacrifice)

Results

- Mortality: None reported.
- Clinical Signs: HD salivation "seen on occasion in LD rats & frequently in other dose groups."
- Body Wt: "No effect in F. 1/5 M at 250 or 500 mpk gained less weight than controls."
- Organ Wt & Gross Pathology: "No effects noted."
- Light Microscopy: "Possible treatment-related changes in liver & kidney. Changes included multifocal hepatocellular degeneration and/or necrosis in 1/5 HD M, individual liver cell necrosis & Kupffer cell proliferation in 1/5 HD F and increased incidence of interstitial nephritis in HD M."

Comments: According to the sponsor, this study "was not conducted to GLP standards." In addition, the actual data from the study were not submitted - only the sponsor's summary.

3-Month Oral Toxicity Study in Rats

Material Tested: DW A5000 61

Species & No. Animals: Charles River CD rats, 12/sex/dose gp

Dosage Levels & Frequency: 0 (distilled water vehicle), 56, 167 & 500 mpk/day in 2 divided doses 6 hrs apart

Results

Mortality: Two LD F (day 61), one MD F (day 18), and one HD M (day 18) were found dead.

Clinical Signs: Occasional yellow staining of anogenital area of HD rats.

Food Intake/Body Wt: Wt gain was less in drug-treated M than in control M (not dose-related); no such effect occurred in F; no wt loss in animals found dead. Drug treatment had no effect on food intake.

Ophthalmoscopic Exam: No treatment-related findings (slit lamp & indirect ophthalmoscope on days 8 & 90).

Hematology; Clin. Chem.: Hgb levels were decreased in HD F, RBC levels were lower than controls in both M & F HD animals. Mean alkaline phos. levels were lower than controls in all drug-treated gps; SGOT & SGPT levels were reduced in LD (M & F) animals.

Organ Wt: Mean liver wts (abs. & rel.) were higher in HD & MD F than in control & LD rats.

Pathology: No drug-related gross or histopathological changes were noted in liver, kidney, or any of the other tissues examined.

Drug Plasma Conc'n: Increased with dose; no evidence of accumulation. Mean level in HD rats was approx. 100-130 (measured on days 2 & 91).

Gross Pathology

End of 4-week Treatment: Hydronephrosis in 2 M (1/12 LD, 1/12 HD)

End of 17-day Recovery: Drug-treated gps were similar to controls.

Histopathology

End of 4-week Treatment:	Control M/8	Control F/8	High Dose M/8	High Dose F/7
Kidney: tubular regen., cortex	1		2	
nephritis, interstitial				1
Uterus: dilated horn				3
Eye: retinal atrophy	1	1	1	
Lung: interstitial pneumonia		1	1	
foreign body granuloma		1	1	
Congestion: thymus	1	1	1	1
Injection Site: perivascular hemorr.	1		1	1
Foci of Perivasculitis	1		1	

Six-Month Oral Toxicity Study: [Performed by Sponsor; sperm evaluation done by

Methods: Charles River CD rats, 12/sex/dose group, were given AZT by gavage at 50, 150 or 500 mpk/day in 2 equal portions 6 hrs apart. Control group received distilled water.

Results:

Mortality: 2-3 rats/group (5 in HD gp) - dosing accident or undetermined cause

Clinical Signs: Salivation post-dose all HD M & F, wks 1-26; also stains on bodies of some HD rats

Body Wt; Food intake: HD M rats gained more wt than controls; all other gps had growth curves similar to controls. Drug had no effect on food intake.

Hematology; Clinical Chemistry: Hct & Hgb decreased slightly in HD F only; RBC decreased & MCV increased in HD M & F. Values returned to normal during post-dose recovery period. Drug had no effect on WBC. Blood glucose was increased in HD M & F; SGOT was elevated in F at all doses.

Ophthalmology: No toxicity was noted.

Drug Plasma Conc'ns: One-half hr after the 2nd daily dose, mean levels of AZT were 4.2, 17.6 & 83.2 on day 2 & 9.7, 34.4 & 142 mcg/ml on day 177 for rats given 50, 150 & 500 mpk, respectively.

Semen Evaluation (Postmortem): No drug effect on parameters monitored (sperm motility, epididymal sperm density, incidence of abnormal sperm).

Organ Wt: At day 57 post-dose (but also at study day +1), there was increased liver wt (abs. & rel.) in HD F.

Gross & Histopathology: In neither the rats found dead nor those at terminal sacrifice were there any remarkable drug-related findings.

Two-week Oral Dose Range-finding in Dogs: (Sponsor's summary submitted to

Doses of 125, 250 & 500 mpk (capsules) were given daily in divided doses, 6 hrs apart, to one M & one F.

The HD F was moribund on day 14. Both HD dogs had emesis with blood. All treated animals had "fecal alterations."

Moderate-marked leukopenia & thrombocytopenia occurred in all dogs; also, erythroid values decreased in all treated dogs.

Histopathology revealed GI hemorrhages at the MD & HD, hypoactivity of lymph nodes at all dose levels, and mild-marked bone marrow hypocellularity at all dose levels.

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2-week Oral Dose Range-Finding Study of BW A509U in Cynomolgus Monkeys (conducted at

Procedure: Four groups of monkeys (1/sex/gp) were dosed for 2 weeks @ 125, 250 or 500 mpk/day orally (gavage) in divided doses, 2x/day; control group received methylcellulose 0.5%.

Results: There was no mortality and the only adverse effect noted was vomiting in the H @ 500 mpk. Weight loss occurred only in the H @ 125 & 250 mpk. RBC, Hgb & Hct were reduced slightly in all drug-treated animals (not dose-related). SPT values were elevated in both HD animals, and in the HD M. Review of the single-page summary of gross pathology findings revealed no apparent drug-related toxicity.

Plasma levels at 30 min. post-morning dose on day 13 (2 animals) averaged 20, 10 & 67 mcg/ml BW A509U @ 125, 250 & 500 mpk, respectively. The glucuronide conc'n was relatively constant, averaging ca. 30 mcg/ml at each level.

Approximately 35% of the administered dose was recovered in urine on either day 1 or 13, slightly more appearing as the glucuronide (60%) than the drug (40%).

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13-Week Oral Toxicity Study in Monkeys

Material Tested: AZT (BW 0509U81)

Species & No. Animals: Cynomolgus monkeys; 4/sex/dose

Dosage Levels & Frequency: 0 (methylcellulose vehicle), 34, 100 & 300 mpk/day for 13 wks, given in 2 equal doses, 6 hrs apart

Results

Mortality: None

Clinical Signs: "Sporadic vomiting in all gps, which did not appear dose-related, except for 1 HD M which vomited during or shortly after almost half of the dose administrations." Also "loose feces in 2 HD animals".

Body Wt: No loss.

Food Intake: "No consistent change" (no data submitted).

Ophthalmoscopy: "Test article....did not cause eye abnormalities" (ophthalmologist's report).

Hematology: There was a dose-related progressive decrease in RBC count throughout the study, while Hgb & Hct dropped between study days 1 & 21 and remained at that level. Mean corpuscular volume rose steadily from day 21. Decreased WBC count occurred, not only in HD M as reported by the sponsor, but also in HD F & MD F. Sporadic increases in platelets occurred in some animals in all drug-treated gps.

Clin. Biochemistry; Gross Pathology; Organ Wts: No treatment-related changes.

Plasma Levels: At 0.5 hr after the AM dose on day 2, mean plasma levels were 4, 5 & 16 mcg/ml for AZT and 12, 15 & 24 mcg/ml for GAZT at 34, 100 & 300 mpk/day, respectively. On day 87, mean values were 5, 8 & 15 mcg/ml for AZT and 15, 19 & 25 mcg/ml for GAZT.

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1. Dose Range-finding Study in Pregnant Rats

Species & No. Animals: CD rats; 8/dose groups

Dosage Levels & Frequency: 0 (deionized water vehicle); BW A 509 U 125, 250 & 500 mpk/day in 2 divided doses, 6 hrs apart, days 6-15 of gestation

Results

Mortality: None

Clinical Signs: Soft feces in 1 MD & 1 HD; salivation in 1 HD rat

Maternal Body Wt: Wt gain comparable in all gps

Maternal Necropsy: "No significant changes observed" in any animal (tissues examined not specified).

Fetal Body Wt: Comparable in all gps

Fetal External Findings: "No remarkable observations" in any animal (no malformations or variations in any of the approx. 80 fetuses/gp).

Embryonic/Fetal Viability: 2 early resorptions in each gp (4 in LD); no dead fetuses, no late resorptions.

2. Dose Range-finding Study in Pregnant Rabbits

Species & No. Animals: NZ white rabbits; 5/dose group

Dosage Levels & Frequency: 0 (0.5% methylcellulose vehicle); BW A 509 U 125, 250 & 500 mpk/day in 2 divided doses, 6 hrs apart, days 6-18 of gestation

Results

Mortality: 2 controls, 1 LD & 2 HD animals died from dosing accidents; 1 HD aborted (sacrificed) on day 22.

Clinical Signs: Gasping for breath noted in 4 controls & 1 HD animal

Maternal Body Wt: Comparing day 29 vs. day 0 data, "mean" wt gain in each gp was approx 600 gm. (See Table 1, attached.)

Maternal Necropsy: "No significant changes observed", including animal that aborted.

Fetal Body Wt: LD & HD comparable to controls; no HD fetuses

Fetal External Findings: "No remarkable observations" in any of the approx. 40 fetuses

Embryonic/Fetal Viability: No dead fetuses, 1 early resorption in each gp (2 in control); 1 late resorption in control gp

3. Oral Teratology Study in Rats:

Species & No. Animals: CD rats; 30/group

Route: Oral (gavage)

Dosage Levels & Frequency: 0 (deionized water vehicle); AZT @ 125, 250 & 500 mpk/day in 2 divided doses, 6 hrs apart, days 6-15 of gestation.

Results

Mortality: None

Clinical Signs: Incidental (e.g., alopecia)

Maternal Body Wt & Food Intake: Comparable in all gps

Maternal Necropsy: "Thoracic and abdominal organs...examined for grossly evident morphological changes"..."maternal tissues that have gross lesio s will be fixed...for histopathological examination only if deemed necessary." However, no data were presented.

Maternal/Fetal Effects, Day 20: No abortions, 90+% gravid; no dead fetuses, only 1 late resorption (LD); fetal wts/lengths comparable in all gps; only 1 abnormality upon visceral exam of fetuses (HD); skeletal exam revealed unossified sternebra (HD) & rudimentary ribs (HD).

Plasma Levels: Using HPLC, mean (n = 3) plasma levels in dams on the 10th day were 41, 83 & 150 mcg/ml for the LD, MD & HD, respectively. Fetal tissue levels (whole body homogenates) were 9.5, 33 & 61 mcg/gm.

4. Segment II Oral Teratology Study In Rabbits: Pregnant NZ white rabbits, 17/group (4/gp for drug plasma evaluation) were administered 0 (0.5% methylcellulose), 50, 150 or 500 mpk/day given as 2 equal portions by gavage, 6 hrs apart, on gestation days 6-18.

Mortality: None drug-related, but 12 due to dosing accidents (includes 2 controls & 6 HD) and one that aborted.

Clinical Signs: "Red material" caused by technical errors; also, labored breathing.

Body Wt; Food Intake: No significant effect.

Maternal Survival/Pregnancy Status: Only 6-8 dams/group with viable fetuses.

Mean Fetal Data: 50% Fewer viable fetuses & implantation sites in the HD than in controls; early resorptions & post-implantation loss higher in LD & MD (but not HD) groups; no dead fetuses in any group; wts of fetuses in all gps were comparable.

Fetal Malformations/Variations: Increased no. of fused sternebrae in the LD only; no visceral findings; bent hyoid arches (LD) & sternebrae #5 and/or #6 unossified (HD).

Plasma levels on the last day of treatment (50, 150, 500 mpk/day orally

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1. Mutagenicity Evaluation

Prof. Rpt. #: TTEP/05/0013

Material Tested: BW dissolved in DMSO

Test System: Mouse lymphoma assay

Activation System: Drug tested in the absence & presence of S9 liver microsomal enzyme preparation from Arochlor-induced rats

Conc'n Tested: 1,000-10,000 ug/ml

Control Compounds

- Negative: DMSO
- Positive: Without metabolic activation - Mycanthone methanesulfonate dissolved in saline; with metabolic activation - 2-AAF in DMSO.

Results

- In the absence of metabolic activation, BW was weakly mutagenic at 4,000 & 5,000 ug/ml after 4 hrs exposure and weakly mutagenic at 600 ug/ml after 24 hrs exposure.
- In the presence of metabolic activation, BW was weakly mutagenic at 1,000-5,000 ug/ml after 4 hrs exposure.

2. Salmonella/Mammalian Microbial Mutagenicity Studies

Using tester strains TA 98, 100, 1535, 1537 & 1538, with & without metabolic activation by Arochlor-induced rat liver microsomes, BW at levels of 0.01-1.0 mcg/plate did not increase the no. of revertants in the Ames assay. Toxicity to the tester strains was noted at levels of 10 mcg/plate and higher.

Using the pre-incubation (20 min.) modification of the Ames test to detect damage that might not be detected by the plate incorporation method, results were as described above.

3. Cell Transformation Assay

This BALB/c-3T3 neoplastic transformation assay was performed according to standard operating procedure. Conc'ns of AZT as low as 0.1 mcg/ml reduced the no. of cells in culture after a 3-day exposure. A stat. sig. increase in the no. of aberrant "foci" was noted at a conc'n of 0.5 mcg/ml. This behavior is characteristic of tumor cells and suggests that AZT may be a potential carcinogen. It appears to be at least as active as the positive control material, methylcholanthrene.

4. Cytogenetic Study in Rats [Culture & dosing done at BW; analyses performed]

Groups of rats (4/sex/gp) were given single doses of 37.5, 75, 150 or 300 mpk AZT IV. Colchicine was given IP 2 hrs prior to sacrifice which was 6, 24 or 48 hrs after the AZT. Negative (saline) & positive (cyclophosphamide) controls were included. Immediately after sacrifice, bone marrow cells were collected from both femurs and processed according to standard techniques for chromosome analysis. Other groups of animals received 0, 37.5, 75, 150 or 300 mpk IV and were sacrificed 5 min. or 4 hrs later for plasma drug conc'n determinations.

There was no increase in structural chromosome aberration frequency at any dose of AZT, relative to controls. Similarly, there was no increase in the percentage of cells with other than 42 chromosomes.

Plasma levels 5 min. after the IV dose were 100, 330, 640 & 1650 micromolar AZT and 10, 17, 20 & 30 micromolar AZT. Four hrs later, the drug had virtually disappeared from the plasma.

5. In Vitro Cytogenetic Study in Cultured Human Lymphocytes

[Conducted by

Blood specimens from 3 healthy human donors were incubated for 24 hrs in a medium containing reconstituted phytohemagglutin. Cells were then exposed to the test article at conc'ns of 250-1000 mcg/ml (0.3-1000 mcg/ml in dose range-finding study using blood from one donor), negative vehicle (DMSO solvent), or pos. control [250 mcg/ml ethylmethanesulfate (EMS)] for 48 hrs. After blocking cell mitosis with colcemid, cells were fixed, stained and those in metaphase analyzed for the presence of structural & numerical cytogenetic abnormalities.

Results: The number of aberrations produced by BW at levels of 250-1000 mcg/ml was equal to approx. 1/2 that produced by the EMS. In addition, some structural damage was noted at levels of 3-100 mcg/ml.

At conc'ns of 30 mcg/ml & above, BW reduced the mitotic index (proportion of cells undergoing mitosis) to the same degree as EMS. Some reduction was noted with conc'ns as low as 1 mcg/ml.

The sponsor states that "increased numerical abnormalities were not observed..." but data were so equivocal that the percentage of nondiploid cells in negative control cultures was similar to that noted for EMS

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Open Label study, past-September 1986

Section 8 contains copies of the slides presented by Dr. King at the Advisory Committee Meeting, as requested.

Section 9 contains information on plasma levels of AZT from patients on Protocol 02, particularly as they relate to body weight and concurrent use of acetaminophen.

Section 10 contains data in support of statements in the NDA which refer to the relative merits of dose reduction and dose interruption for hematologic toxicity.

Section 11 contains a formal safety update to the NDA.

Sections 1 and 2: Open Label Extension Trial of AZT (Protocol 08 Following Placebo-Controlled Trial (Protocol 02)

Immediately following the recommendation of the Data Safety Monitoring Board on September 18, 1986 to discontinue the placebo arm of the AZT trial, the principal investigators were contacted with instructions to call in their patients, inform them of whether they had been on AZT or placebo, and offer them the option of enrolling in an uncontrolled trial of open label AZT at a dose of 200 mg every 4 hours, slightly lower than the dose studied in the placebo controlled trial (the sponsor was concerned about the hematologic toxicity of 250 mg q 4 h and felt that production of 100 mg capsules would provide greater flexibility in dosing).

Thus, essentially two new open label uncontrolled trials of AZT were initiated, both in well characterized groups of patients with many months of baseline data. The first "trial" consists of continued dosing of the original group of AZT recipients from the placebo-controlled trial, and is important in that it provides data on a reasonably large group of carefully studied patients treated with AZT for longer than four months. Although there is no longer a concurrent placebo control group, a substantial number of these patients began treatment within a few months of their first diagnosis of PCP. Therefore their survival can be compared to historical controls although many uncertainties exist with this kind of analysis, due in part to changes over time in the medical diagnosis and treatment of many AIDS-associated complications including the treatment of PCP itself.

The second "trial" within this open label extension protocol consists of the group of patients who were randomized to receive placebo in the controlled trial and then begun on AZT. Therefore, they constitute a group of AIDS/late ARC patients who were presumably at a more advanced stage of HIV-disease at the beginning of AZT treatment than the original AZT recipients in the controlled trial. Again, there is no concurrent control group to which the data can be compared, but this group of patients beginning AZT can be compared to their own baseline data, which is extensive, and also to the first months treatment of the original AZT recipients, realizing that the original placebo patients were at a more advanced stage of disease than the original AZT patients entering Protocol 02. (However, it must be remembered that the members of the original placebo group entering Protocol 08 were a select group of "survivors" from the original group of placebo recipients enrolled in Protocol 02, and therefore may not be that much "sicker" than the original AZT

group.) Data from these patients provide important new information on how well a group of "sicker" patients tolerates AZT and whether there is a pattern of reduction in OI's/death that is similar to that seen in the original AZT group.

One hundred twenty-seven patients originally assigned to AZT in the placebo controlled trial elected to continue taking AZT under the open label extension protocol. These patients were officially entered into the new protocol (08) over a two week period beginning on September 20 (referred to as the "transition" period). Because of the sponsor's concern about the toxicity of AZT, those patients who were still on full doses (250 mg q 4 h) were all reduced to a dose of 100 mg q 4 h. About 3 weeks later the dose was increased to 200 mg q 4 h in those patients who had previously tolerated full doses of 250 mg q 4 h. (200 mg q 4 h was also the dose that patients were to receive under the newly created Treatment IND).

At the time this group of original AZT recipients entered Protocol 08, 61% had AIDS/OI and 39% were still ARC patients by the current CDC definition. The average T_4 count at entry to Protocol 08 was 146/mm^3 (compared to 127/mm^3 for the same patients at entry into Protocol 02) with 75% of patients having T_4 counts less than 200/mm^3.

As of December 23, 1986, the sponsor's cutoff date for submission of data from Protocol 03 to the NDA on January 12, 1987 (4 days prior to the Advisory Committee Meeting on AZT), six additional original AZT patients had died (one apparently a suicide) for a total of seven deaths in this group.

Two of the other 4 deaths occurred in patients who had only received 2 days and 32 days of AZT in the 02 protocol (both were discontinued early secondary to development of an OI). As of approximately February 13, 1987, the most recent "cutoff" date for a telephone survey of the investigators to collect data on deaths and OI's which had occurred on this protocol since December 23, 1986, four more deaths were reported, including another suicide. Thus, of the original 144 patients randomized to AZT, eleven were known to have died. Except for the two suicides (details not submitted), all deaths were secondary to infectious complications of AIDS.

As discussed earlier in the original review of this NDA, 24 patients originally assigned to AZT in 02 had developed OI's as of September 20, 1986, 12 of which had occurred during the first four weeks of treatment. As of December 23, 1986, according to the sponsor, twenty-seven new OI's had been diagnosed in patients during Protocol 08 who were in the original AZT group. (Seven of these 27 new OI's occurred in patients who had already developed an OI during 02; therefore 20 additional patients developed an OI for the first time while on AZT, based on the data available to the sponsor as of December 23, 1986). Twelve of the 27 original AZT patients who developed OI's during Protocol 08 as of December 23 had been on reduced doses or off of AZT at some time during Protocol 02.

As of February 13, 1987, eight weeks later, a total of 64 of the original AZT group were known to have developed at least one OI while on AZT (24 during Protocol 02, 20 additional patients as of December 23, 1986, and 20 more as of February 13, 1987). Of these 64 patients, 9 had developed two OI's while on AZT, two had three OI's, and one patient had 4 OI's diagnosed while on AZT, for a total of 76 OI's occurring in patients receiving AZT since the beginning of Protocol 02. (51 of these OI's occurred on 08; 27 in the first 3 months and 24 in the subsequent 2 months).

The distribution of deaths and OI's by time on AZT is displayed in a block diagram prepared by the sponsor at my request (see following page). As can be seen, following the first month of therapy with AZT, the number of OI's is minimal up until week 10 of treatment, after which the incidence of OI's increased substantially (this is approximately the same time the placebo arm of Protocol 02 was discontinued). Of concern is whether this increased incidence of OI's will be reflected in a substantially increased risk of death in the near future. Only 11 patients of the original 144 AZT recipients were known to have died as of February 13, 1987.

N=100 One hundred (100) patients originally assigned to placebo in Protocol 02 elected to begin treatment with AZT under the open label extension trial in late September 1986. Because of concern about the toxicity of AZT, the sponsor chose to use a dose of 200 mg q 4 h instead of 250 mg q 4 h.

At the time these patients were started on AZT, 64% had AIDS/OI and 36% still had ARC. Their mean T_4 count at entry into Protocol 08 was 115/mm^3 with 81% of the patients having a T_4 count <200/mm^3.

As of December 23, 1986, 13 more patients from the original placebo group had died, in addition to the 19 reported in the original NDA. Four of these 13 additional deaths occurred during the "transition period" after September 20 but before the patients had actually started taking AZT. Thus these four deaths occurred before initiation of AZT treatment. The remaining nine deaths occurred on AZT, seven during the first four weeks of treatment and the other two at week 8 (HIV encephalopathy) and week 10 (respiratory failure).

As of February 13, 1987, three additional patients on AZT had died from the original placebo group, two from PCP after sixteen and 19 weeks on AZT, respectively, and the third at an undocumented date with possible cause listed as toxoplasmosis. Thus, as of February 13, 1987, a total of 35 deaths were known to have occurred in the original placebo group; 23 before AZT was begun, started, seven of infections diagnosed during the first 4 weeks on AZT, and five at a later time.

As discussed in the original medical review of this NDA, 45 patients assigned to placebo in Protocol 02 were known to have developed OI's as of September 20, 1986, twelve of which were diagnosed during the first 4 weeks of therapy. Included in these 45 patients were 4 who had developed two OI's each during the placebo-controlled trial. Nine additional patients (eight of whom subsequently died of their OI) had developed an OI while on placebo but were not yet reported at the time the NDA was prepared. Thus 54 of the original placebo patients had developed OI's before they began AZT. Eighteen additional patients developed OI's while on Protocol 08, eight of which

occurred during the first 4 weeks of AZT treatment (eleven others occurred in patients who had had an OI previously reported while on Protocol 02.)

The distribution of OI's and deaths in the original placebo group can be seen in the two block diagrams on the following pages (prepared by the sponsor at my request). The first one shows events occurring in this group of patients while on placebo and also after beginning AZT (pink). The other block diagram shows events occurring in these patients only after beginning taking AZT. As can be seen on the last chart, there was a clear decrease in the incidence of death and OI's over time after the first month of therapy.

The data on deaths and OI's collected by the sponsor over the telephone during the week following February 13, 1987 are still "preliminary" and subject to verification. Nevertheless, it would appear that the following conclusions can be drawn from the data available at this time:

1) After 18 weeks of therapy, the incidence of OI's and deaths increased in the original AZT group. It is unclear whether the temporary (three week) dose reduction in these patients to 100 mg q4h contributed to this increase, but the greater risk has persisted well beyond that period.

2) The total number of deaths (12) in the original AZT group is still lower after nine months of treatment than the number of deaths (23) in the original placebo group after four and a half months in the placebo controlled trial.

3) The original placebo group appeared to be "sicker" at the time protocol 08 began than the original AZT group at the beginning of the placebo-controlled trial in terms of the proportion of patients with AIDS and the time since diagnosis of first episode of PCP in those with a history of this infection. The mean T4 cell count in the placebo group at the start of AZT therapy (115/mm^3) was not much lower than that in the original AZT group at the beginning of the placebo-controlled trial (122/mm^3), however.

4) The original placebo group appeared to experience a beneficial effect from AZT after starting therapy in that the incidence of OI's and deaths declined after the first month of therapy. Although there is no concurrent control group, this appears to be a real effect of the drug because the risk of these events was much higher in the month before the placebo controlled trial was discontinued and during the first month on AZT. This pattern of clinically evident benefit following the first month of therapy was also seen in the original AZT group.

Thus it appears that the efficacy of AZT continues beyond the 18 weeks of treatment which occurred during the placebo controlled trial, although the data accumulated since that time indicate that patients are experiencing OI's and death at an increasing rate. AZT treatment in the original placebo group has resulted in an apparent benefit to these patients as well in terms of a reduction in the risk of OI's and death after four weeks of therapy, even at the slightly lower dose of 200 mg q4h. Prolonged follow-up of these patients is essential in order to better determine how long the efficacy of AZT will last.

Section 3 contains charts displaying the number of patients who received concomitant therapy with acyclovir, ketoconazole, aspirin-containing products, acetaminophen-containing products, and trimethoprim/sulfamethoxazole. (TMP-SMX) and the duration of such therapy.

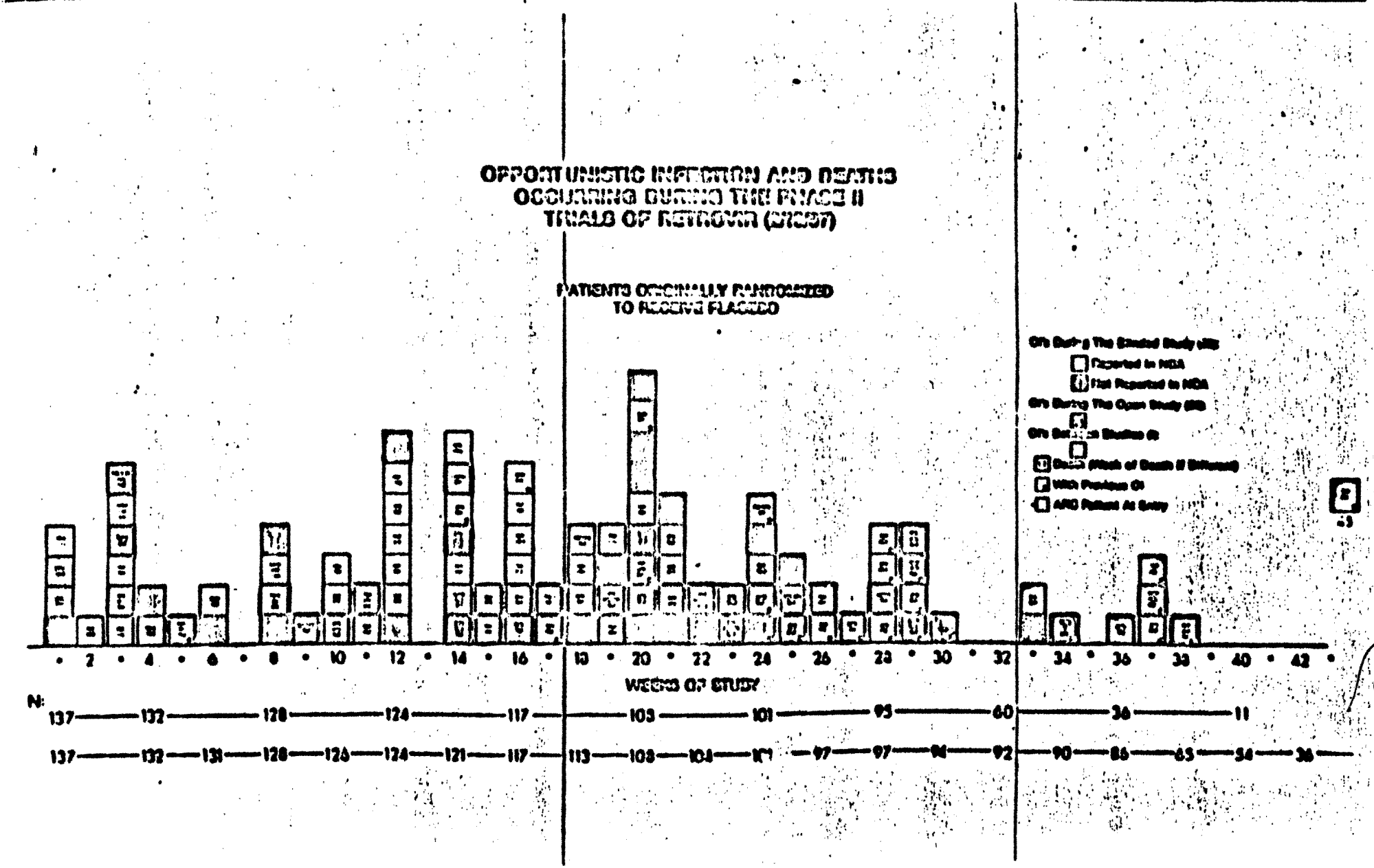
There is no striking difference between the treatment groups in either the number of patients receiving concomitant medications, or in the duration of such exposure. In fact, the placebo group received slightly more concomitant therapy with these drugs.

Section 4 contains a tabulation of the 12 patients (3 AZT, 9 placebo) who received more than 2 weeks of systemic acyclovir therapy and also developed an OI. The number of such patients are too small to draw any conclusions regarding the possible role of acyclovir in increasing the efficacy of AZT (44 patients overall received at least 2 weeks of systemic acyclovir treatment).

Section 5 contains hard copy of the data from Protocol 03 supplied on floppy disk to the statisticians. In addition, bar charts were submitted showing the incidence of hemoglobin (< 7.5 gm/dl) and neutrophil ($< 750/mm^3$) toxicity by four-week intervals, and the frequency of transfusions for patients in both groups after beginning AZT.

For the original AZT group the peak frequency (10% of patients) of hemoglobin toxicity occurred at 9-12 weeks. (see chart on page 10 of this review).

After sixteen weeks, the majority of occurrences of this toxicity were in patients with a prior occurrence of hemoglobin < 7.5 gm/dl. For the original placebo group after beginning AZT, the peak frequency (7%) of this toxicity occurred during the first four weeks of therapy, with new patients developing this toxicity for the first time after 16 weeks (numbers are small, however; see chart on page 11)


OPPORTUNISTIC INFECTION AND DEATHS
OCCURRING DURING THE PHASE II
TRIALS OF RETROVIR (AZT)
PATIENTS ORIGINALLY RANDOMIZED
TO RECEIVE PLACEBO
2
4
6
8
10
12
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24
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28
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32
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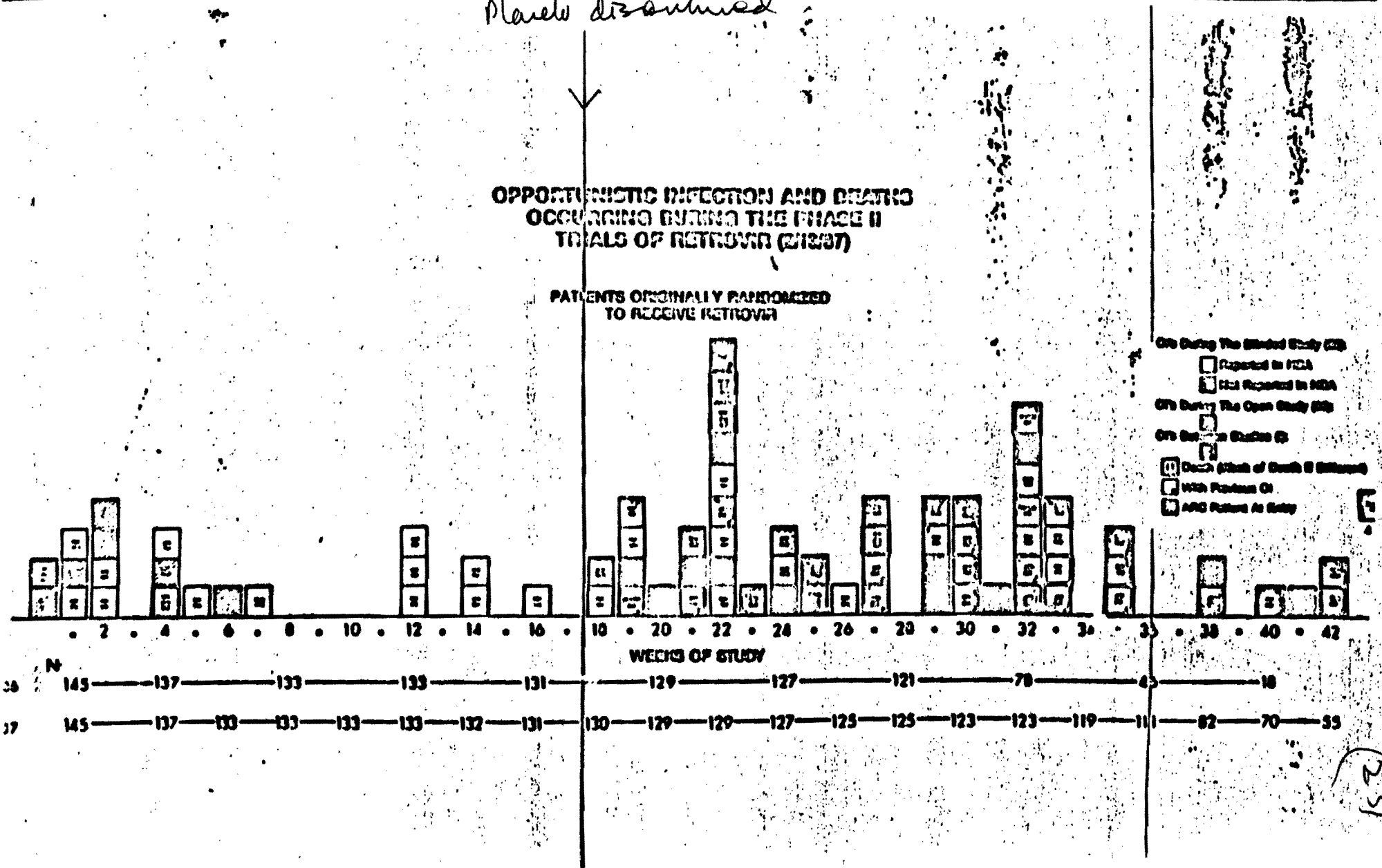
36
38
40
42
WEEKS OF STUDY
N:
137 132 128 124 117 103 101 95 60 36 11
137 132 131 128 126 124 121 117 113 108 104 97 97 96 92 90 86 65 54 36

Placebo discontinued

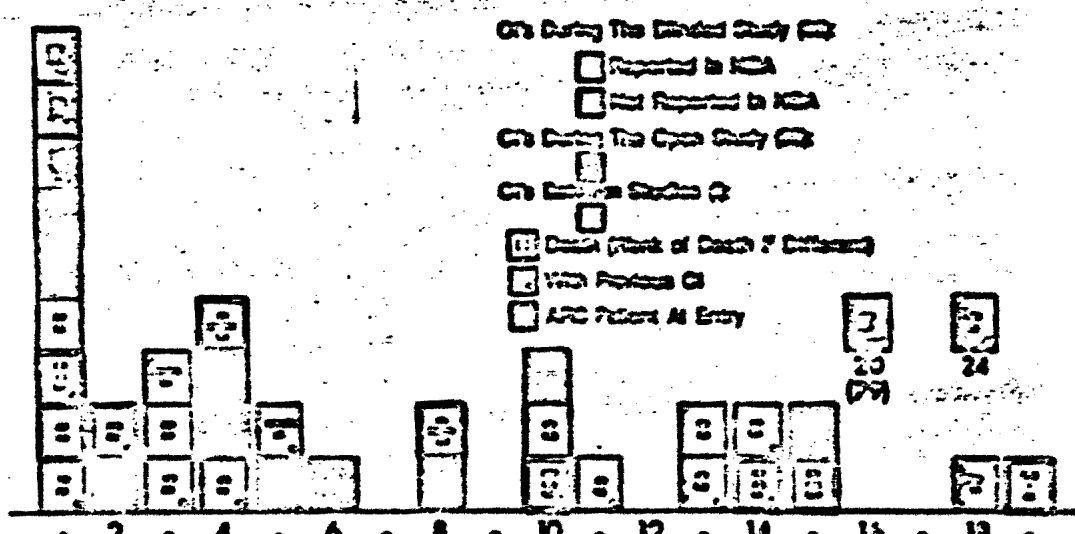


(23)

OPPORTUNISTIC INFECTION AND DEATHS OCCURRING DURING THE PHASE II TRIALS OF RETROVIR (AS307)

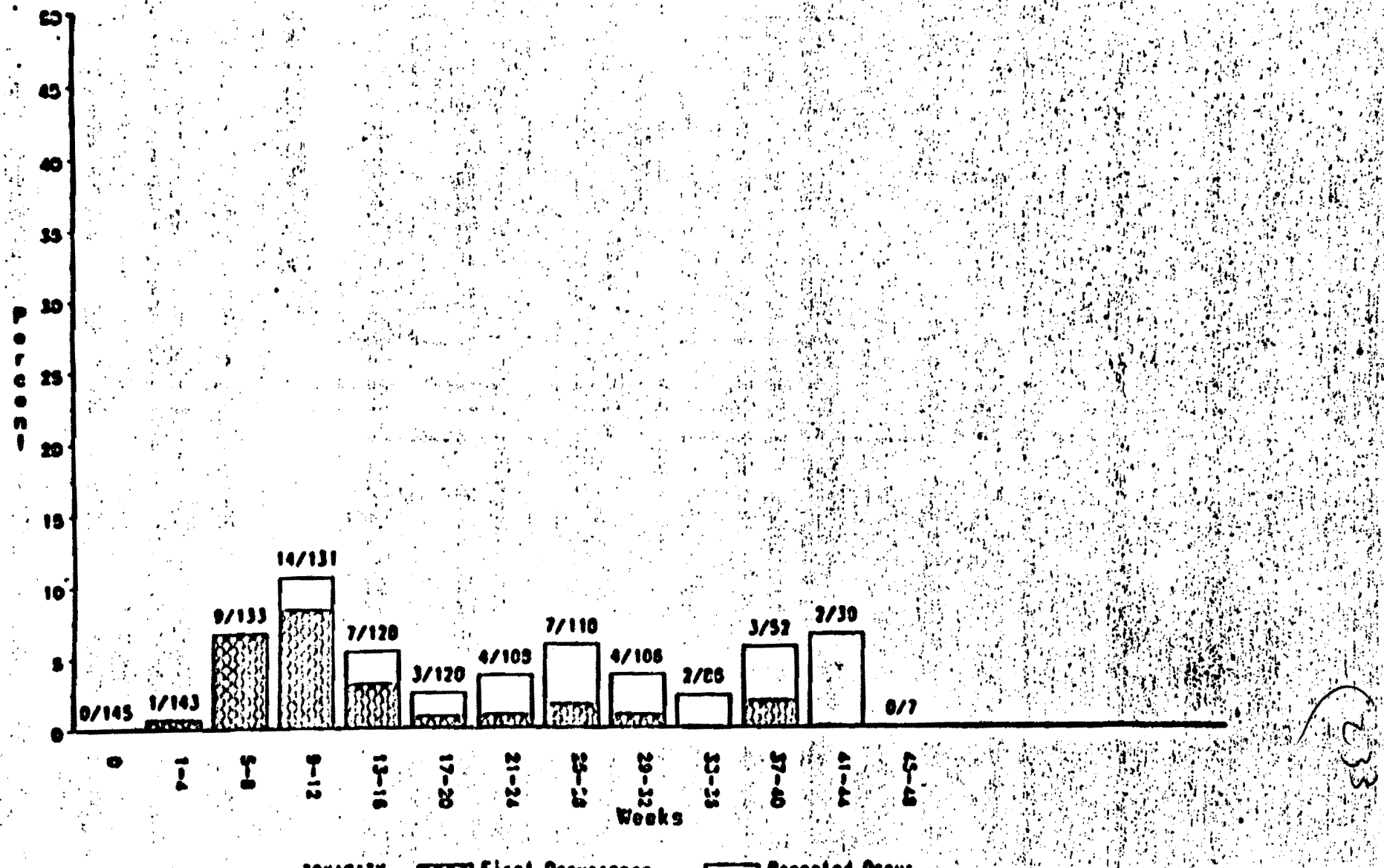
PATIENTS ORIGINALLY RANDOMIZED TO RECEIVE PLACEBO

OPEN STUDY

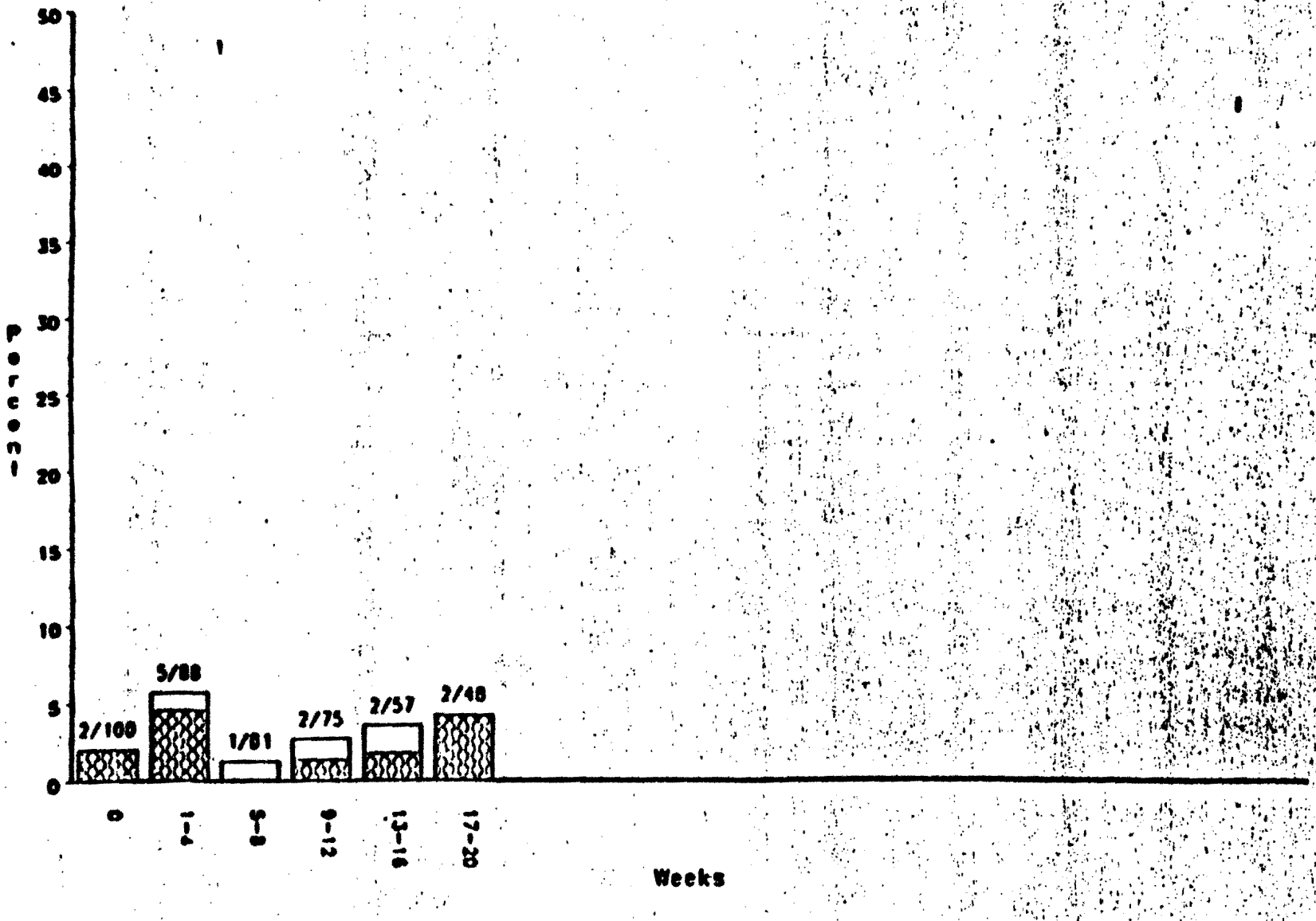


	N							
10/30/86	93	91	91	90	87	83	67	
2/13/87	93	91	92	91	90	87	83	83	83

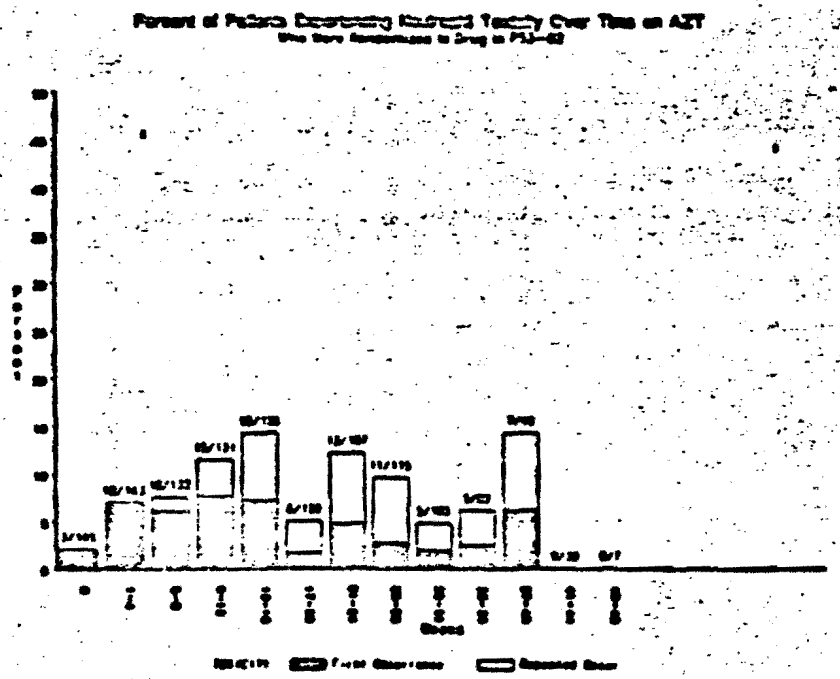
Percent of Patients Experiencing HCD Toxicity Over Time on AZT
Who Were Randomized to Drug in PES-02



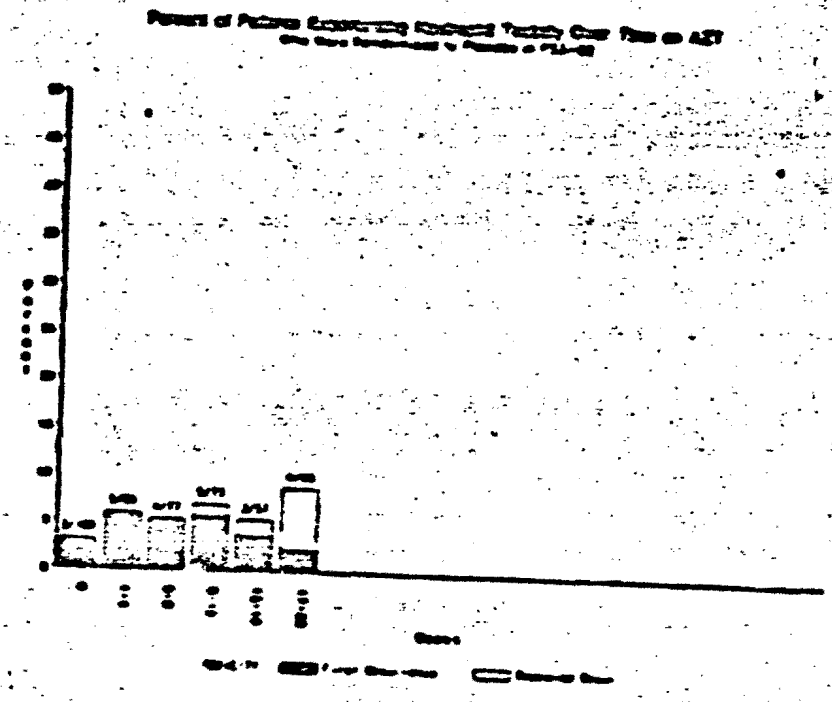
Percent of Patients Experiencing HSD Toxicity Over Time on AZT
Who Were Randomized to Placebo in P53-02



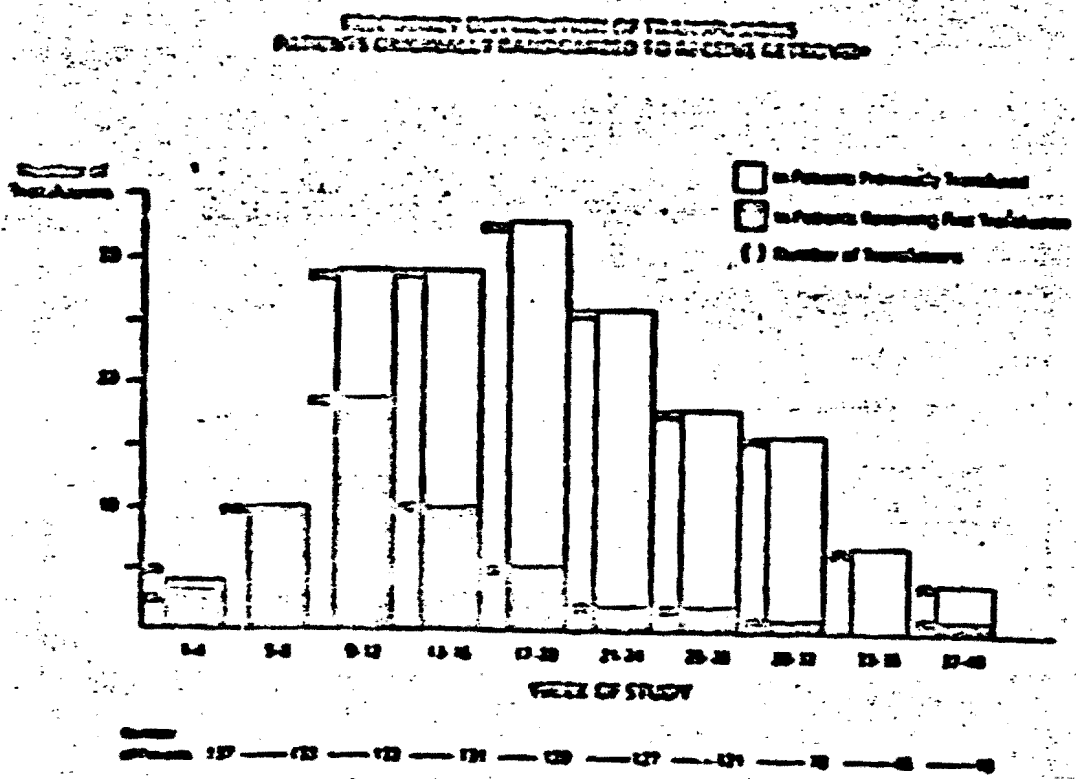
For neutrophil toxicity, the peak incidence in the original AZT group (almost 15%) occurred at the 13-16 week interval, as seen in the chart below. Nearly as high a proportion of patients developed this toxicity at 21-24 weeks and 37-40 weeks as well, over half being "repeaters."



For the original placebo group, between 5 and 10% of patients at all time intervals (up to 20 weeks) developed this degree of granulocytopenia, as seen below.

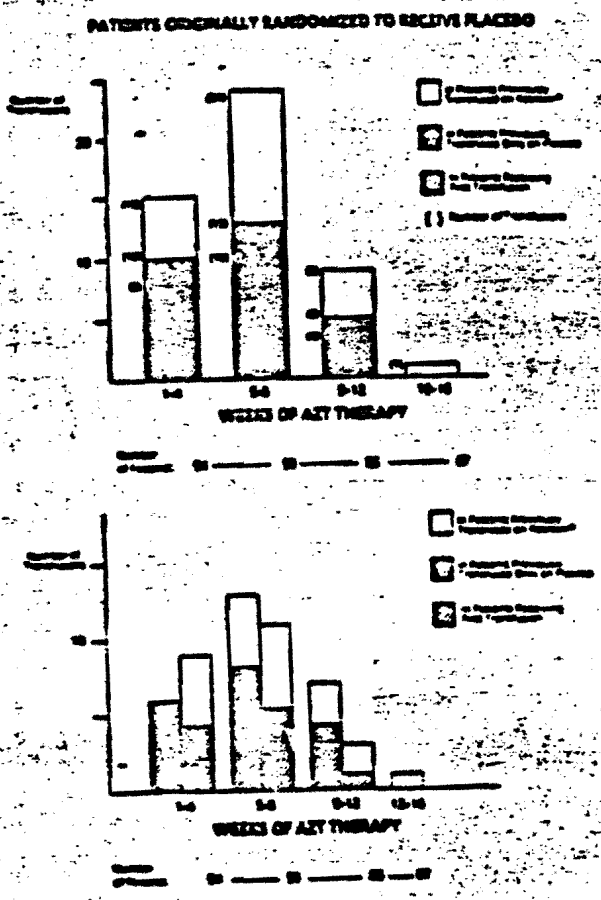


The frequency distribution of patients receiving transfusions among the originally AZT group indicates that transfusions were administered as early as the first month of treatment. A rapid increase to approximately 20-25% of patients receiving transfusions per 4-week interval occurred after 8 weeks of therapy, as seen in the chart below.



After 16 weeks, the vast majority of transfusions were in patients who had had previous transfusions.

For the original placebo group who received AZT, a larger proportion of patients received transfusions earlier in the course of therapy (16% during first month, 27% during the second month), dropping to 10% during the third month and less than 2% (one transfusion) during the fourth month.



This accelerated early rate of transfusions compared to the original AZT group may reflect the greater susceptibility of these "sicker" patients to hematologic toxicity after beginning AZT, and also an increased awareness on the part of the investigators of the hematologic toxicity of the drug, resulting in a decreased threshold for transfusion therapy.

The sponsor also submitted plots of mean T_4 cell counts in patients originally randomized to AZT who completed at least 28 weeks of therapy. The number of patients providing data ranges from 98 at week 0 to 38 at week 28. It is not clear why there are data on only a subset of patients, even during the placebo controlled portion of the trial.) These plots (reproduced on the following three pages) reflect an initial rise in T_4 counts at week 4 followed by a drop in AIDS and low T_4 at entry groups, and values in ARC and high T_4 at entry groups that are close at 24-28 weeks to what they were at entry. In the low T_4 count at entry subgroup, the mean at 28 weeks is actually less than it was at entry.

Pages 17-19 (240
Not supplied by FDA

T4 lower at 78 wk
than at earlier

For patients in the original placebo group who were started on AZT, an initial rise in mean T_4 count is not discernable for all patients (as seen on t 2 page 21) or for any of the subgroups.

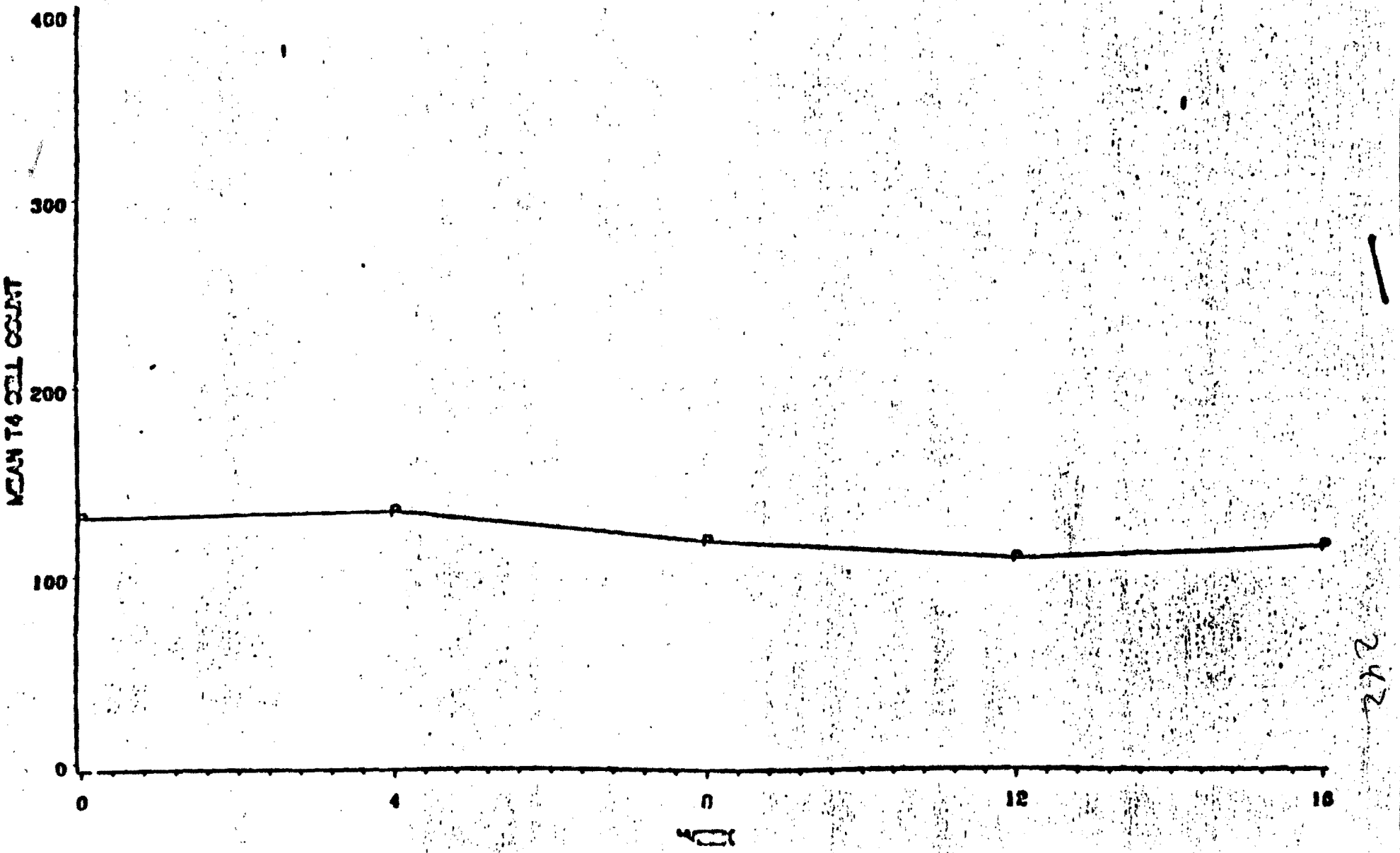
The number of patients providing data for these means range from 105 at entry to 81 at week 16.

Thus it may be that "sicker" patients do not experience the initial boost in T_4 cell counts that was seen in patients in the original AZT group.

MEAN T4 CELL COUNT FOR PATIENTS IN STUDY AT LEAST 10 WEEKS

Patients Randomized to Placebo in P53-02

All Patients



So where the hell is the "accompanying life table"?

152/4175 = 4% in 2 months (243

Section 6 At FDA request, the sponsor submitted survival curves and accompanying life tables from the Treatment IND data for reports of all deaths received up to and including February 17, 1987. The sponsor notes that the database used in this analysis is not quality assured and is incomplete in many respects, e.g. information on drug start date was absent for approximately 1/4 of the patients and was estimated by using the date of data entry for initial registration form plus 2 days.

The sponsor constructed survival curves of the proportion of patients surviving after AZT treatment including and excluding deaths occurring in the first 28 days, and a curve showing the proportion of patients surviving after PCP infection. The curve for patients surviving after AZT treatment is steeper for the first 28 days and then breaks to a more shallow downward slope out to 115 days, which is the longest duration of AZT therapy reported in these patients (94% surviving). The number of patients at risk at each time point is recorded in the accompanying life table. (4175 patients entered, 3196 at risk at 28 days, 2552 at 8 weeks, 1505 at 12 weeks and 146 at 16 weeks.) One hundred patients died during the first month, 52 in the second month. The survival curve of patients surviving excluding deaths in the first 28 days indicates that 97% of patients were alive at 105 days. A disproportionate number of deaths occurred during the first 28 days, probably reflecting mortality in premorbid patients who were begun on AZT "in desperation," and also because the beneficial effects of AZT are generally not seen clinically until after approximately a month of treatment (data from placebo-controlled trial).

100/3196 = 3.1% — 100/4175 = 2.4 — These bastards are concealing data !!! — = 112 days

A third survival curve was submitted showing the proportion of patients surviving after confirmed PCP infection, and indicates 75% survival 700 days after confirmed PCP infection. This analysis is not very meaningful in that patients were started on AZT at many different times following their episode of confirmed PCP, and the confirmed episode (requested on the Patient Registration Form for the Treatment IND) is not necessarily the first episode. Also, patients who died shortly after an episode of PCP are not included in this analysis since they never had a chance to enroll in the Treatment IND. Therefore this survival curve does not help clarify either the efficacy or safety of AZT in the Treatment IND setting.

what!?

The sponsor also included a summary of activity under the Treatment IND indicating that as of March 3, 1987, 4387 patients had received zidovudine and 6253 renewals had been received and drug shipped.

100/3196 + 52/2552 = 4% (5% in first 2 months!)

~~105 days = 15 weeks~~

97% − 4% (1st month) 93% alive

6% mortality in 15 weeks??

Why the hell don't they just give the # of deaths first, and then go into their goddamn curves! 11574

Median ... 7.3

4175/2 = 2088

The sponsor also submitted a summary of adverse events resulting in hospitalization reported in patients enrolled in the Treatment IND. One hundred and thirty-seven patients reported such events including 47 with fever, 32 with hematologic toxicity, 23 with neurologic events, 19 with gastrointestinal complaints, and four or less each with genitourinary, cardiovascular, endocrine, skin, or general body complaints. It is impossible to determine from these listings whether the adverse event was due to zidovudine, or what the likelihood of possible drug association was, according to the treating physician's judgment. The hematologic problems were likely due to the drug, as they are similar to those seen in the controlled trial, i.e. 13 anemia alone, 7 leukopenia (2 also with anemia), four granulocytopenia (2 also with thrombocytopenia) and 8 pancytopenia. It is not reported whether or not blood counts returned to baseline after discontinuation of zidovudine, assuming that dose modification occurred.

Nausea and vomiting were the most common gastrointestinal complaints. Seizures and confusion were the most common neurologic adverse events.

Section 7 of this submission includes an update on the analysis of the virology data from the placebo-controlled trial. The update includes HIV culture results for patients entered at all study sites (the original NDA submission reported the culture results from one center only, that of Dr. Fischl at the University of Miami), and additional data documenting changes overtime in p24 gag protein antigen levels in the serum of patients enrolled in the trial.

As related in the original NDA of this NDA, HIV cultures were performed on all patients twice pre-entry and every 4 weeks thereafter by monitoring cultured lymphocytes from patients for levels for reverse transcriptase activity in supernatant fluid. "In most cases, absolute values for reverse transcriptase activity were recorded and the cultures were scored as positive or negative according to conventions established by each virologist. The day of culture on which the specimen was first postive was also noted. The data were then analyzed using Cochran-Mantel-Haenszel statistics."

Specimens from 5 of the study sites were sent to a single virology lab and cultured there. Apparently there were fewer results per patients than from the other study sites, and the results were reported in a different format, so the sponsor chose to analyze the data from these centers separately. Their conclusion is that "no statistically significant differences in ability to recover virus over the course of the trial were detected in AZT treated patients compared to placebo patients."

The results of virus cultures from the remaining centers, including that of Dr. Fischl, were analyzed separately. Culture results for all AZT treated patients were compared to those for all placebo recipients. No statistically significant differences could be seen between the groups although there was a trend toward significance at week 20 (17/33 AZT recipients with negative culture compared to 5/19 placebo recipients). Since the p-values for the differences between the treatment groups at all the preceding intervals ranged from p=.873 (pre-entry) to p=.493 (at 16 weeks), it is unclear whether the

p value of p=.033 at 20 weeks suggests antiviral activity of AZT or is a statistical artifact. At week 24, the p value is 0.031 but is based on small numbers (7/14 negative cultures in the AZT group compared with 3/11 negative in the placebo group.)

Virus culture results for these seven centers were also analyzed by grouping patients by entry T_4 cell number and by diagnosis of AIDS or ARC at enrollment. All comparison between treatment groups for each of these subgroups were not significant, with the exception of the patients with < 100 T_4 cells at entry at week 4 (p=.037; 10/16 AZT recipients with negative cultures compared to 3/12 placebo recipients). Whether or not this is a real finding reflecting antiviral activity of AZT needs confirmation, as 28 comparisons were done in these subgroup analyses, and therefore at least one "significant" results at the p<.05 level would be expected.

According to the sponsor, over 600 (frozen) serum samples from 157 patients enrolled at seven study sites were submitted to Abbott Laboratories for determination of serum p24 antigen levels using their enzyme linked assay kit recently approved for research use in the United States. "This analysis was undertaken to try to confirm the observation of Chaisson et al that administration of AZT was associated with significantly decreased amounts of virus-coded protein compared to levels documented in placebo recipients. Thirty-six AZT patients and 40 patients in the placebo group were found to have detectable serum p24 antigen. Of these patients 28, in each group had both entry serum and a later specimen available to evaluate changes in antigen level. The data from these 56 patients were analyzed using Wilcoxon Rank Sum Tests," and are summarized in the table below.

Table 2
CHANGES IN MEDIAN SERUM p24 ANTIGEN LEVELS
AZT PLACEBO-CONTROLLED TRIAL

WEEK	AZT			PLACEBO			p Value for Change From Baseline
	n	Median	Mean	n	Median	Mean	
0	28	163	297	28	100	234	—
4	28	42	70	28	73	223	.0002
8	26	33	56	23	90	283	<.0001
12	16	39	53	13	63	84	.0052
16	7	60	105	11	219	499	—
20	4	113	177	3	1113	837	—
24	2	179	179	—	—	—	—

(244

"Statistically significant decreases from baseline serum p24 antigen were documented for AZT recipients or week 4 (p=.0002), week 8 (p< .0001) and week 12 (p=.0052). These differences were most marked for those patients who entered the study with low T_4 cells or with the diagnosis of AIDS .... Antigen levels in placebo patients were lower than those in the AZT recipients. In most cases the levels were stable over the course of the trial or rose slightly.

"These data indicated that administration of AZT is associated with statistically significant decreases in serum p24 antigen levels. However, the precise relationship of decreased antigen detection in serum an in vivo antiviral effect is not known. Decreased ability to detect antigen may be indicative of a decrease in the amount of free plasma virus and may thus reflect true antiviral activity of AZT in man. Alternatively, decreases in plasma antigen levels may mean that AZT administration has improved the patients' immune competence resulting in increased antibody levels and decreased ability to detect antigen in the face of continued virus replication. The relationship of changing serum p24 antigen levels to clinical outcome or changes in laboratory parameters such as T_4 cell number or delayed type hypersensitivty responses remains to be determined. Analysis of these associations may allow correlation of the clinical benefits of greater survival, decreased incidence of opportunistic infections, and improved sense of well being observed in this study with specific changes in levels of virus replication or changes in immune response to HIV infection."

The sponsor has subaitted a reasonable interpretation of the possible significance of these new virology results in the preceding paragraph.

No change in T_4
despite probable antiviral
activity.

Section 7 of this submission also includes a preliminary report by Frederick A. Schmitt, Ph.D., of the Department of Neurology at the University of Kentucky Medical Center, consultant to Burroughs Wellcome entitled "Neuropsychological Assessment of Patients in a Multi-Center Placebo-Controlled Trial to Evaluate Azidothymidine in the Treatment of Human Immunodeficiency Virus."

A battery of neuropsychiatric tests were administered to patients enrolled in the trial pre-entry, and at 8 week intervals thereafter. The tests consisted of number of well-established measures of affective and cognitive functioning, which have been used extensively in evaluating the neuropsychiatric effects of other drugs.

It is well established at this time that central nervous system disease is commonly associated with HIV infection, with neurological symptoms including dementia, memory dysfunction, and concentration problems as well as other cognitive changes. Motor disturbance and psychiatric symptoms such as depression, organic affective syndrome, anxiety, and apathy are also not uncommon features. Neuropsychological testing would appear to be important in identifying intellectual and motor impairment in AIDS and ARC patients that may not be found in routine mental status evaluation, and to follow this aspect of clinical well-being in response to drug treatment.

The objectives of this aspect of the protocol, specified retrospectively, were

1. To characterize the cognitive changes associated with HIV infections in patients with AIDS Related Complex (ARC) or Acquired Immune Deficiency Syndrome (AIDS).

2. To relate observed cognitive changes to measures of drug response and toxicity.

3. To characterize personality factors related to drug response and/or toxicity.

Dr. Schmitt states that the results reported at this time "are considered to be preliminary in nature, as the data have not been completed, checked and verified, nor have reliability estimates of the various scoring procedures been completed at the present time. Further, given the large number of variables derived from each of the affective and cognitive measures, only a subset of variables are reported in this section."

Pre-entry and baseline scores indicate that "both AZT and placebo patients were comparable on the various measures of interest," and that performance fell well within the normal range for each of the measures assessed.

For affective measures, there was little difference between the AZT and placebo groups over the course of the study. Patients receiving AZT showed a relative reduction in severity of distress when compared to the placebo group, at both 8 and 16 weeks, which was entirely accounted for by differences among AIDS and low T_4 at entry patients. Lower fatigue symptoms and increased vigor were reported in AZT recipients compared to placebo at week 8 in all patients, AIDS and those with T_4 counts $< 100/mm^3$ at entry, but not at week 16.

Review of the cognitive measures reveals more consistent and more statistically significant drug effects than were seen for the affective measures. "In general, the cognitive measures reflect little change from baseline or some decline for patients receiving placebo. On the other hand, patients receiving AZT appeared to show improvements over baseline for attention, memory, visuo-perceptual, visual scanning, and mental and motor speed. The positive effects of AZT are most consistent for those patients with the AIDS diagnosis and those patients with low T_4 cell counts on entry into the therapeutic trial."

Dr. Schmitt concludes his report with the following:

"Clearly, additional analyses of the neuropsychological data are warranted given the relative positive effects seen in cognitive functioning as a result of drug treatment. It is quite possible that the effects seen on both affective and cognitive measures are mediated somewhat by the general level of functioning of patients at entry. As a result, correlational analyses between Karnofsky performance levels at entry and later change from baseline in both affective and cognitive functioning may help clarify the pattern of differences seen in the current analyses. Further, analysis of confounding factors such as the existence of an opportunistic infection at the time of assessment, as well as other possible confounds, will be attempted. Overall, the pattern of data from the neuropsychological measures is consistent with the data reported for the Karnofsky scores. Generally, significant improvement in performance from baseline can be seen at week 8 and is maintained or increases at week 16 for AZT patients in comparison to controls. These differences appear to be due to relative improvement over baseline in the drug group as well as some deterioration in the functioning of placebo patients."

Dr. Schmitt's assessment appears to accurately reflect the data analyses provided in this submission.

As in Section 7, a copy of an internal Burroughs Wellcome memo was submitted which was written in response to a request by this reviewer to clarify which opportunistic infections that were reported were not actually documented by laboratory methods. According to the author of this memo, Dr. Drucker, eleven placebo and three AZT recipients had unconfirmed infections, nine of which were recurrent episodes of PCP.

Section 8 containing copies of the slides shown by Dr. King at the Advisory Committee meeting does not require a review.

Section 9 states that no additional information on plasma levels of AZT, particularly as they relate to body weight and the concurrent use of acetaminophen, were available.

Section 10 consists of the data tabulations which were used to discuss dose modifications in response to hematologic toxicity in the original NDA. Patients were classified according to the reported initial dose modification (i.e. dose reduction or discontinuation). The sponsor states, "Because management of each patient was dependent upon the judgment of the primary physician and because criteria for dose reductions and discontinuation of therapy served only as guidelines, dosing changes in response to toxicity were not consistent. Only very general statements may be made regarding the relative merits of dose discontinuation compared to dose reduction."

According to these tabulations, 73 patients in the AZT group had dose modifications during the placebo-controlled trial (as of September 22, 1986), 42 of which were to manage hematologic toxicity. Twenty-four (24) of these patients were permanently discontinued and not restarted; 5 for administrative reasons, 11 for opportunistic infections, two for minor medical reasons, and six for hematologic toxicity (4 anemia, 1 neutropenia, and one combination). Fourteen patients were initially discontinued and then restarted, eight because of hematologic toxicity, seven of whom were restarted at a lower dose (q 8 h). Five of these eight were due to anemia, four of whom required transfusions. Thirteen patients were changed to a lower dose (q 8 h schedule) as their first dose modification and then maintained at that dose. Nine of these were due to anemia, all but one of whom required transfusions and 5 of whom also had neutropenia, and four for neutropenia alone, all of whom experienced increased granulocyte counts on the reduced dose. Twenty-two patients were changed to q 8 h dosing initially, and then the dose was further modified. Nineteen of these patients had dose changes in response to hematologic toxicity, 12 with anemia only and 7 with other hematologic toxicity or in combination with anemia. Seventeen of the nineteen patients eventually had drug discontinued (15 of whom later were restarted at q 8 h and

2 who were permanently discontinued). The other 2 of the 19 had neutropenia alone which resolved on the reduced dose and dosing these patients was increased back to a q 4 h schedule.

As noted by the sponsor, it is impossible to draw any firm conclusions regarding the relative merits of dose modification alternatives from this data. However, the following observations can be made:

1. Nearly all the patients who had dose modifications for anemia were also transfused, regardless of whether AZT was discontinued or reduced. (The one patient in this category who did not receive any transfusions was an ARC patient with T_4 >100/mm^3 at entry who was initially taken off drug because of the anemia).

2. All patients who were dose reduced for anemia were eventually taken off the drug for some period of time anyway. If RBC toxicity is severe enough to require transfusions, dose reduction instead of initial dose interruption does not appear to be of benefit in permitting marrow recovery.

Nine additional patients with anemia were managed with transfusion alone, i.e. without dose modification. Two of these patients developed OI within 6 weeks of beginning AZT, and none developed OI's thereafter. This is compared to 11/37 transfused patients who developed OI's (two of which occurred within the first 6 weeks of therapy) who were also dose modified. Eight of these remaining nine OI's apparently occurred following extended periods of dose modification and interrruption of therapy.

These data suggest that perhaps repeated transfusions while maintaining full doses of AZT is the preferable alternative for managing RBC toxicity. This approach runs the risk of accelerated toxicity, however. If dose modification appears necessary, the above data suggest that AZT should be discontinued temporarily, as dose reduction does not permit adequate marrow recovery to occur. These suggestions must be taken only as hypotheses in need of confirmation, as firm conclusions can not be drawn from this type of data (e.g. it may be that there was a bias towards managing anemia in the "healthier" patients with transfusions alone, while the "sicker" patients also received dose modifications.)

A clinical study in which patients who develop anemia are randomized to alternative methods for managing the anemia is needed. Perhaps some patients can be managed with transfusion alone while others will require dose interruption. Identifying predictors of response would be very useful, as would monitoring "viral load" as a surrogate for efficacy in patients undergoing dose modification in response to toxicity.

Neutropenia without anemia tended to be managed with dose reduction or a short (one week) interruption of therapy followed by dose reduction. It is not clear from the small number of patients (six) managed in this way whether a longer dose interruption followed by restoration of full doses would be possible or preferable or whether patients would become granulocytopenic again after full dosing was restarted. Again, a study to address this issue while monitoring "viral load" as a surrogate for efficacy is needed.

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Section 11 of this submission contains the "formal safety update" to the NDA requested in our letter of February 25, 1987 to Burroughs Wellcome. It consists of one paragraph referring to their submission of January 12, 1987, and a statement claiming that safety data acquired since that date have been reviewed and no safety concerns were found which are not clearly defined in their proposed labeling of December 2, 1986. The Agency had agreed that such a short statement would suffice, but that a list of the trials from which safety data were reviewed should be included. This list was provided in their March 16, 1987 submission which contains their response to our approvable letter of March 9, 1987.

Ellen C. Cooper, M.D.

Ellen C. Cooper, M.D.

cc:
Orig NDA 19-655
HFN-830
HFN-815
HFN-815/CSO/JKnight
HFN-815/ECCooper:bam:3/19/87:2185m

Addendum + follow-up materials (252

(253)

Addendum #1 to Medical Officer Review of NDA 19,655-

March 16, 1987

Sponsor: Burroughs Wellcome Company
3030 Cornwallis Road
Research Triangle Park, N.C.

Drug: Retrovir (zidovudine) 100 mg capsules

In this addendum to my MOR of this NDA dated March 9,1987, the results of FDA inspections of the twelve study centers which participated in the single multicenter trial which was submitted in support of this NDA will be addressed. In addition, the issue of individual patient exclusions will be briefly discussed.

For most of the medical centers which participated in the multicenter trial, only minor deviations from standard protocol procedures were noted in the FDA inspectors' reports. Therefore, VAI2 letters (outlining the items of concern and thanking the investigator for his/her cooperation during the inspection) were issued by the Division of Scientific Investigations to six of the centers, and apparently similar letters will be sent to four more centers shortly (based on a telephone conversation today with Mr. Antione El Kage from the Office of Compliance). At one center, that of Margaret Fischl at the University of Miami, no problems or concerns were identified, and an NAI (no official action) letter was sent. However, problems were observed at one center, that of Dr. Robert Schooley at Massachusetts General Hospital in Boston, shortly after the NDA was submitted. The FDA inspector found multiple deviations from standard protocol procedure, and she recommended that data from this center be excluded from the analysis of the multicenter trial.

QUOTE

In late December, 1986, after personnel in the Center for Drugs and Biologics became aware of the problems seen at this center and received a copy of the Form FDA 483 issued to Dr. Schooley at the conclusion of the inspection, the decision was made to request inspection of all twelve centers which participated in this trial, due to the importance of this drug, its high public visibility, and because one of the early inspections had revealed "significant deviations" from FDA regulations regarding the proper conduct of clinical investigations.

also late!

locking the barn after the horse is stole — 3 months after trial was terminated

The Establishment Inspection Report (EIR) from the Schooley center was not available to the Division of Anti-infective Drug Products until January 7, 1987. At that time, it was felt that there was not adequate time to fully address the issue and come to a decision before the scheduled January 16, 1987 Advisory Committee meeting on AZT, and it would be very difficult to reschedule the Advisory Committee meeting on such short notice should a decision to exclude the Schooley data appear necessary. Therefore, a meeting was scheduled to address this issue for the following week which was "snowed out" and had to be rescheduled for January 30, 1987. This meeting was attended by members of the Division of Anti-Infective Drug Products, the

rather late, considering study was long terminated

(254

If drug accountability is less than perfect, it is a "serious problem"

Office of Compliance, and by Drs. Parham, Ember and Bilstad at the Center Office level (see minutes of this meeting prepared by J. Knight). Briefly, it was agreed that 1) drug accountability did not appear to be a serious concern, based on additional data and documentation supplied by the company in a submission to the NDA dated January 28, 1987, 2) there was no evidence of falsification of data or intent to bias the results, and 3) although there were numerous deviations from standard procedure for the proper conduct of clinical trials, no one of these deviations appeared egregious enough by itself to warrant exclusion of all the data from this center from the database for the entire trial.

The consensus at the end of the meeting was that the decision as to whether or not the Schooley data should be included or excluded from the database was a "close call", but that, all things considered, the recommendation to the Commissioner should be to include the center. The Commissioner was briefed the following workday morning about the issues discussed at the meeting and the conclusions reached. He felt strongly that before the Agency made a final decision on this highly visible, potentially inflammatory issue, a meeting between Agency representatives, including the Commissioner, and the principal investigators from the center in question should be arranged as soon as possible and any outstanding concerns addressed on a person to person basis. This meeting was held on February 11, 1987, and representatives from Burroughs Wellcome were also present (see minutes of this meeting by Mary Gross of the Commissioner's staff). The earlier recommendation to include the data was confirmed, pending resolution of some minor discrepancies in the drug accountability records, and submission of hospital records on some of the patients enrolled at the center. The drug accountability concern was resolved satisfactorily in a small meeting between Dr. Bilstad, the FDA inspector, Ms. Patricia Spittig, and representatives from Burroughs Wellcome which took place immediately after the larger meeting. Dr. Schooley gathered and submitted on March 6, 1987 the discharge summaries from patients hospitalized during the trial. Review of these records reveals no major discrepancies from the information recorded on the Data Collection Forms submitted with the NDA.

At the January 30, 1987 in-house meeting, the possibility of excluding data from individual patients in whom protocol violations were noted was briefly discussed. Apparently this is a common practice in the review of many NDAs, both in the Division of Anti-infective Drug Products and in other divisions. This reviewer noted that if exclusion of all patients with protocol violations were strictly applied, quite a few patents would probably be deleted from the database. It would also be difficult to determine in some instances whether a protocol violation actually occurred, since there was considerable latitude for investigator discretion in managing the patients, and the Case Report Forms were not well designed to document when, why and with whose authorization discretionary patient management decisions were made (e.g. there was no standard method for performing dose adjustments; concomitant medications were frequently prescribed, despite a general prohibition against them in the original protocol). No decision was actually made as to whether individual patient exclusions should be considered, however.

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NDA 19-655 - 3 -

Later, following another in-house meeting on February 10, 1987 at which other concerns regarding review of the NDA were also addressed (see minutes by J. Knight), it was decided that review of the NDA should proceed without individual patient exclusions. Because the mortality analyses were so strongly in favor of the drug, any slight biases that may have been introduced when minor "protocol violations" occurred were highly unlikely to influence the outcome.

Therefore, the NDA was reviewed including the data from all patients at all twelve centers as originally submitted by the sponsor.

Ellen C. Cooper, M.D.

Ellen C. Cooper, M.D.

cc:
Original NDA
HFD-015
HFD-240
HFD-015/DD
HFD-015/Cooper:3/16/87
015

CRAP! It is a matter of principle that you do not retain false data & that you do not mix in garbage with good data.

(256

Addendum #2 to NDA of NDA 19-655

March 17, 1987

Sponsor: Burroughs Wellcome Company
3030 Cornwallis Road
Research Triangle park, N.C.

Drug: Retrovir (zidovudine) 100 mg. capsules

In this addendum, I will briefly review the data submitted by the sponsor to the NDA on March 13, 1987. This material was submitted in response to requests contained in a letter from Dr. Tabor dated February 25, 1987, and deals largely with data from the open label extension protocol of zidovudine which was offered to all participants in the placebo-controlled trial after the placebo arm was discontinued on September 18, 1986. Some of this material was sent to this reviewer as desk copies prior to completion of the original medical review of this NDA (dated March 9, 1987), and a preliminary assessment of the deaths and opportunistic infections (OI's) is contained under Item 15 of the Summary and Conclusions section of the review.

Section 1 of this 2 volume submission contains tabular listings of patients who died or developed OI's in Protocol 02 (the placebo-controlled study) or Protocol 08 (the open label extension study). In addition, a listing of patients who developed KS or other AIDS-associated malignancies was provided. Item 2 contains block charts displaying deaths and OI's by week on study for placebo recipients and zidovudine recipients in both Protocol 02 and 08, as requested.

Section 3 contains tables in which the number of weeks of concomitant drug therapy in both the placebo and zidovudine groups during Protocol 02 are depicted for five drugs - acyclovir, ketoconazole, aspirin, acetaminophen, and trimethoprim/sulfamethoxazole, as requested.

Section 4 lists patients who had received concomitant acyclovir during Protocol 02 who also developed an OI, and the week of onset.

Section 5 contains hard copy of the data from Protocol 08 (demographics at entry, T_4 counts, time to OI's, time to death, hemoglobins, etc.) which was requested in the February 25 letter. This data was also submitted on floppy disc to be analyzed by FDA statisticans. Charts were also submitted displaying percentage of patients developing anemia and granulocytopenia by 4-weekly intervals during both Protocols 02 and 08, the percentage of patients receiving blood transfusions by 4-weekly intervals , and plots displaying means of T_4 cell counts.

Section 6 contains information related to the company's treatment IND for AZT which was approved in late September 1986, under which more than 4000 AIDS patients with a history of PCP have been receiving AZT.

Section 7 contains additional virology data from the placebo controlled trial, the results of neuropsychiatric testing presented by Dr. Schmitt at the Advisory Committee Meeting on January 16, 1987, and a list of patients in whom the diagnosis of an OI was not confirmed by culture or histology.

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March 18, 1987

Addendum #3 to Medical Officer's Review of NDA 19-655

Sponsor: Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, N.C. 27709

Name of Drug: RETROVIR (zidovudine) 100 mg Capsules

In this review, I will address Burroughs Wellcome's response to the Agency's March 9, 1987, approvable letter regarding this NDA. The sponsor submitted responses on March 16 and March 18, 1987.

The March 16 letter responds to all the conditions specified in the approvable letter.

1. Labeling. Twelve copies of final printed labeling were submitted. The contents are acceptable, as previously agreed. The understanding stated by the company that "certain adult patients" in the Indications section does not exclude adolescent patients over the age of twelve years is also acceptable. The size of the print is too small, however, and should be reset in larger type.

2. Follow-up data. This refers to data requested in the February 25, 1987, letter from Dr. Tabor to Dr. Lyon of Burroughs Wellcome. These data were formally submitted to the Agency on March 13, 1987, and are reviewed by this Medical Officer in Addendum #2 of the Medical Officer's Review of NDA 19-655. The submission if acceptable.

3. Post-marketing Studies (animal). The response to these requests was submitted on March 13, 1987, and has been reviewed by Dr. Chernov and found acceptable.

4. Post-marketing Studies (human).

   a. 1) Post-marketing surveillance for safety.

   Two draft protocols were submitted describing studies agreed to in concept at a March 13, 1987 meeting between representatives of the FDA and Burroughs Wellcome. These protocols were reviewed by this medical officer and Dr. Joel Kuritsky of the Division of Drug and Biologic Product Experience, Office of Epidemiology and Biometry, and are approvable in concept as stated in Dr. Kuritsky's memo to Dr. Tabor dated March 18, 1987. The company should submit quarterly reports from both studies to the NDA as well as to the Division of Drug and Biologic Product Experience.

(218

a 2.) Follow-up of patients enrolled in Protocol 03.

The company has agreed to follow these patients for continued efficacy and safety data for a minimum of two more years, and periodically report appropriate summary statistics to the Agency. Protocol 03 will be amended to reflect this commitment and should include, at a minimum, the same parameters that are currently being monitored in Protocol 08. Quarterly reports of the data and appropriate analyses should be submitted to the NDA.

b. 1) Studies in patients not included in the approvable indications.

The initial response (in the March 16, 1987 submission) to this condition of approval was inadequate. Four studies were listed; two in patients with AIDS-Dementia Complex and two Phase I/early Phase II trials in which the combination of zidovudine and acyclovir are to be studied in asymptomatic HIV-infected patients and patients with early AIDS. The Agency had verbally communicated to Burroughs Wellcome in the March 13, 1987 meeting that commitments to conduct randomized, placebo-controlled trials of zidovudine alone in asymptomatic HIV-infected patients and in patients with early AIDS were required.

After further discussions between this medical officer and Drs. Dennis King and George Lyon of Burroughs Wellcome on March 16 and 17, 1987, the company agreed in a letter to Dr. Tabor dated March 18, 1987, to commit an adequate supply of zidovudine to conduct the requested studies. It is clearly understood by all parties that the NIH/NIAID AIDS Program will likely sponsor these studies through their AIDS Treatment and Evaluation Unit contracts.

The March 18, 1987 letter from the company constitutes an adequate response to this condition of approval.

b. 2) A study of alternative methods to manage hematologic toxicity.

The company's response to this request will require further discussion before draft protocol(s) are submitted. Amending an ongoing study as suggested by the company is not appropriate.

The company has verbally agreed to discuss this request further with Agency representatives and conduct a mutually acceptable study.

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b. 3) The requested pharmacokinetics/bioavailability study of the commercial 100 mg capsule has apparently already been performed. The company has agreed to submit the data to the Agency within 30 days of approval of the NDA.

5. Safety Update. Reviewed as part of March 13, 1987 submission and found acceptable.

The initial promotional material submitted with the March 16, 1987, response to the approvable letter is unacceptable to this medical officer and in need of substantial revision.

Ellen C. Cooper, M.D.

cc:
Orig NDA
HFN-815
HFN-815/CSO
HFN-840
HFN-815/ECooper:js/3/19/87
2137a

(260

(267

Division of Anti-Infective
Drug Products
Chemist's Review #1
Date Completed: 1/7/87

A.1. NDA 19-655

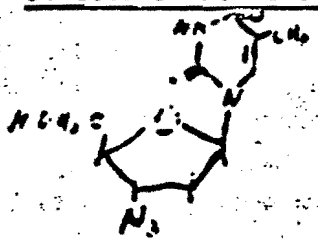
Sponsor: Burroughs Wellcome Co.
Research Triangle Park, NC 27709

2. Product Names: USAN, INN: zidovudine
Proprietary: Retrovir
Other: AZT, BW A509U

3. Dosage Form & Route of Administration: Oral hard gelatin capsules 100 mg, 250 mg.

4. Pharmacological Category and/or Principal Indication: AIDS treatment.

5. Structural Formula and Chemical Name's):



3'-azido-3'-deoxy-thymidine

B. 1. Initial Submission: 10/17/86

2. Current amendment (controls): 10/22/86 (2); 11/13/86; 12/11/86; 12/19/86; 1/7/87 (2); 1/23/87; 1/29/87

3. Related Documents:

4. DMF's:

C. Remarks:

This is an unusual application in that rapid clinical acceptance has required the sponsor to go from pilot synthetic lots to full scale production. The relatively broad specifications for the new drug substance and dosage forms are probably required to assure that production requirements can be met. This reviewer sees no realistic dangers in the proposed specifications, although refinement as experience is gained will be attempted.

The limited available stability data have been balanced by the sponsor's commitments to submit data quarterly and to waive their right to extend dating pending a first annual assessment. Based on precedent with "generic drugs" and existing data, an 18 mo. expiry is acceptable on a tentative basis.

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D. Conclusion:
The application is approvable from the manufacture and controls viewpoint subject to the following conditions:

1. Blister pack labeling is revised to incorporate a "Protect from Light" warning. Container labeling should include "Dispense in Light Resistant Containers per USP.

   The appropriate USAN name should be employed in conjunction with the trade name.

2. Impurity profiles for the first ten (10) full scale production lots of the n.d.s. from each facility are submitted as available (with quarterly reports) to permit adjustment of specifications if requisite. (precedent exists with "generic" drugs.)

3. Quarterly stability reports for the dosage forms are provided.

4. * The research studies on the fate of the cleavage products of azidothymidine are provided with the (acute) animal studies as soon as possible, at least with the first annual report.

Under the above conditions and based on submitted data, the reviewer concludes that a reasonable chemical "benefit to risk" ratio is achieved.

John W. Taylor, Ph.D.

cc: Orig. NDA
HFN-815 HFN-815/CSO HFN-815/Taylor: 1/20/87
HFN-815/MO R/D initialed by: ARCasola 1/20/87 ARC 2/3/87
0551c

* Addendum to review: 1/28/87 acute animal studies were provided and hand delivered to the reviewing pharmacologist. Cleavage products are as yet not identified, but at proposed regulatory limits should not nearly approach those levels utilized for animal studies.

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Review Notes:

182. Components & Composition:

A. mg/capsule	100 mg	250 mg
zidovudine; azidothymidine	100	250
corn starch, NF		
magnesium stearate, NF		
microcrystalline cellulose, NF		
sodium starch glycolate, NF		

Capsule shells: (as amended 12/1986)

100 mg white opaque (TiO_2) caps with YSC 100 in black edible ink dark blue (FD&C #2) band

250 mg light blue/white opaque (FD&C blue #.2 with TiO_2) with H_2F 250 in black ink - seal band as above

184. Facilities, Personnel:
Both N.D.S. and the dosage forms may be produced at either the sponsor's Greensville, NC or Dartford, Kent, England facility.

5. Synthesis:
Attached in summary form with annotations re in-process controls. The sponsor has amended the process to include at least reasonable development standards based on intermediate histories.

The synthesis reworks "A" and "B" are now supported with relevant data indicating workability. However, it is not apparent that rework of lots containing the levels proposed under item 5 seem liberal. The recrystallization procedure to decrease does of course lower yields of the drug product. According to the 1/23/87 amendment sponsor is researching methods to reduce levels of the via removing possible at stage 3.

(269

6. Controls (M.D.S.) as amended:

a) Excipients: Per compendium
b) Capsule shells: typical
adequate

c) n.d.s. - 12/11/85
IR ca KBr vs. stnd.
HPLC - retention time

Purity
TLC:

Assay: 97-102% volatile free

Comments:
There is insufficient data to define the sensitivity of the non-UV TLC test. The sponsor commits to animal studies with a degraded solution and is synthesizing the cleavage product for stability studies. Submitted data indicates a complex profile for the

nder autoclave conditions as determined by head space analysis.

It should be noted that although
has not been reduced.

Conclusion:
Reviewer suggests that the sponsor submit impurity profiles and a consistent definition of manufacturing parameters (e.g. any reworks or differences in reaction conditions) for first ten lots of; at each facility with a commitment to revise specifications as additional experience becomes available. It was suggested to the sponsor's representative on 12/12//85, (Mr. Keirnan) that we (FDA) would prefer limits as a reasonable point to be reached.

deletion

(265)

While such a submission request is unusual for an NDA, owing to the necessity for the drug in an invariably fatal disease, balance must be achieved between reasonable specifications and limited production must be balanced chemically against the "benefit" of providing the drug in reasonable quantities.

7. Other Firms: None

8. Manufacturing & Processing:
for the 100 mg and or the 250 mg is proposed.

A rework procedure is provided for capsules failing weight variation. This procedure now is clarified as follows:

1) No excipients are to be added.

2) ca 97% of the gelatin is recovered.

3) Dissolution will be obtained at S_2 levels and a Macon capsule weight machine will be employed.

4) A separate lot number and separate stability protocols will be instituted.

Owing to the short supply of the drug, the reviewer recommends acceptance of the rework procedure under the stipulated conditions.

9. Container/Closure Systems:
a) blister packages

b)

(268

10. Dosage Forms:

A. 100 mg.

ID-UV vs. standard (performed with all assays
TLC Rf matches standard (performed with UV assay and auto analyzer assay).
HPLC (regulatory) - retention time matches std.

dissolution: alt Q= 75% @ 45 min.
unweighted capsules: water; 50 rpm; paddle

content uniformity: USP
Assay: 90-110% by UV or HPLC

Sponsor will add "(regulatory)" clarification (concurrent note by Mr. Kiernan on 1/11/87 discussion with Dr. Taylor). The TLC identity is also a limit test for performed with the UV assay.

B. 250 mg as above. Weight variation per USP is performed.

Comparative data were submitted with the original application demonstrating comparability of the UV, auto analyzer, and HPLC assay methods as well as the adequacy/comparability of the HPLC/TLC identity limit tests. The HPLC assay will be employed as the regulatory method (see p 55) as required by this reviewer.

The former FTIR method was dropped due to non-specificity.

11. Packaging and Labeling: Satisfactory.

12. Stability: Unsatisfactory.

A. New Drug Substance:

a) 5 month data at 30°C, 40°C indicate no degradation.

b) 3 month 60°C/75% RH possible 2% degradation

c) Both UV and fluorescent light I mo indicate fairly rapid degradation - 92% UV/95.2% fluorescent vs a 99% initial value.

d) Excipient compatability: Similar studies on combinations with the commerical excipient formulation indicate UV light sensitivity.

e) 60°C/2 hr studies were conducted with water/0.1N HCl/NaOH and 3.0% peroxide.

(267

UV fluorescent light studies were also performed. Results indicate fo

recovery by . The unidentified components are presumably observed with fluorescent light (3000 f candles). (70% recovery).

Conclusion:
KS is reasonably stable if protected from light and moisture and stored below 30°C. Marked UV/fluorescent light sensitivity is noted. Oxidation potential judged by this reviewer to be minimal.

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B. Results on Dosage Forms as Formulated for Marketing

Lot #	100 mg Container/Closure	Rx data	Comments
GM0315	100 HDPE/tin	3 wks 40°C/75% RH 3 wks 50°C	ca 95% dissolution
GM0316	as above with CRC	as above	as above
GM0315	blister	as above	ca 100% dissolution
612745	100 HDPE/CRC	2 wks 50°C	99.5% dissolution as above
612745	blister	as above	as above
612745	100 HDPE/CRC	1 wks 50°C	95.5-100.3% dissolved
612745	blister	none	

2 wk data 50°C are submitted for the 200 mg capsule. Similar data. Dissolution values 80%.

(269

Suportive data on the Investigational Formulation

Stabilty data for old clinical formulation without

100 mg

Batch	Study No.
682742	12-DF-209
6F2704	12-D-330

Lot 682742 HDPE with CRC cap
Initial 102.3% assay — av. dissolution 99% 45 min
3 mo 50°C 105.5 HPLC — av. 91% 45 min
degradates: initial 0.14%
3 mo. 50°C 0.9%

Lot 682704 blister
Assay initial 100.7% — av. dissolution 83.1%
5 wks 40°C/75% RH 103.7 — 78.1 repeat min
5 wks 50°C 102.2 — 73.7%
* 14 day UV 93.5 — p300349
* 14 day fluor 94.5 — * light protection required!

14 day UV 0.5%; does not match assay.*

250 mg (all in HDPE

Batch	Study No.
5J6001	12-DN-4
5J2708	12-D-17
5L2703	12-D-92
6A2712	12-D-107
682740	12-D-172
542706	12-D-312

100N-4 Tinplate cap bottle 50

Assays	Dissolution
Initial 99.2	av. 88.7 45 min
12 mo 30°C 101.7	80.0
6 mo. 40°C 101.4	85.3
3 mo 40°C 75% RH 97.0	
6 mo. 40°C 75% RH 100.4	
4 wks 50°C 100.2	
3 mo 50°C 98.8/99.3 HPLC/FTIR 83.3D	

degradates initial N/D
12 mo 30°C N/D

Comments: No trend apparent. Slight - in dissolution.

(270

120-17 CRC closure/30

Assays	Dissolution	Degradates
Initial 103.1	91.3	0
9 mo 30°C 103.8/104/3	90.3	0
7 wks 50°C 103.2		0
3 mo 50°C 103.3		0
6 mo. 40°C 75% RH 100.4		

120-92 CRC 30's

Assays	Dissolution	Degradates
Initial 99.2	87.3	none
8 mo 30°C 101.3	86.6/85.7 repeat	none
7 wks 50°C 100.9	75.90 4mo	not reported

120-107 30's CRC

Assays	Dissolution	Degradates
Initial 99.7	87.3	n/d
3 mo 40/75% RH 101.5	(93.4,3 mo 50°C)	.14%
7 wks 50°C 99.2		n/d

120-172 30's CRC

Assays	Dissolution	Degradates
Initial 100.2	102	.33%
3 mo 40/75% RH 101.5	(93.4,3 mo 50°C)	.28%
4 mo 50 101.2 FTIR(nonspecific) 3 mo. 98.7		*1.23% (uncorrecte .5x E valu

120-312 30's CRC

Assays	Dissolution	Degradates
Initial 99.7	92.2	0
5 wks 50°C 105.7		0

Overall Conclusion:
The paucity of data does not permit a useful statistical analysis. No general trends are apparent. With the addition of the
the dissolution should easily meet the Q75% demanded.
indicate no problem with degradates anticipated.

CENSORED

The firm has waived the right to extend expiry, and agreed to submit data quarterly intervals.

Light protection is required for blister packs. Firm should either revise sleeve labeling to indicate this, or preferably utilize
or equivalent. The HDPE container labeling should include "Dispense in t light-resistant contains per USP."

13. Control Numbers: Adequate.

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14. Validation:
Methods were validated without unusual difficulty at DDA, St. Louis. The only major question raised was whether a helix weight should be utilized sink the capsules. Before capsule rupture no dissolution occurs. BW did use helices thus dissolution values are higher than with the weights. Si all data were obtained without weights or helices, this reviewer believes data are adequate for control purposes. The other comment re catalogue t of TLC plate will be relayed to the sponsor for future correction. The H for the [redacted] meets current limits. B-W will provide our labs at request (see 1/7/87 commitment).

15. Inspections:
Per attached the [redacted] The inspection is pending a final report; no problems were noted.

16. Evironmental Impact: None anticipated at the Bureau level.

17. Labeling:
The labeling should list the new USAN name in conjunction with the trade name. "Protect from Light" and "Dispense in Light-Resistant Container pe USP" should be added to the blister & bottles, respectively.

18. GLP: Conformace cited.

19. Biovailability: Required.

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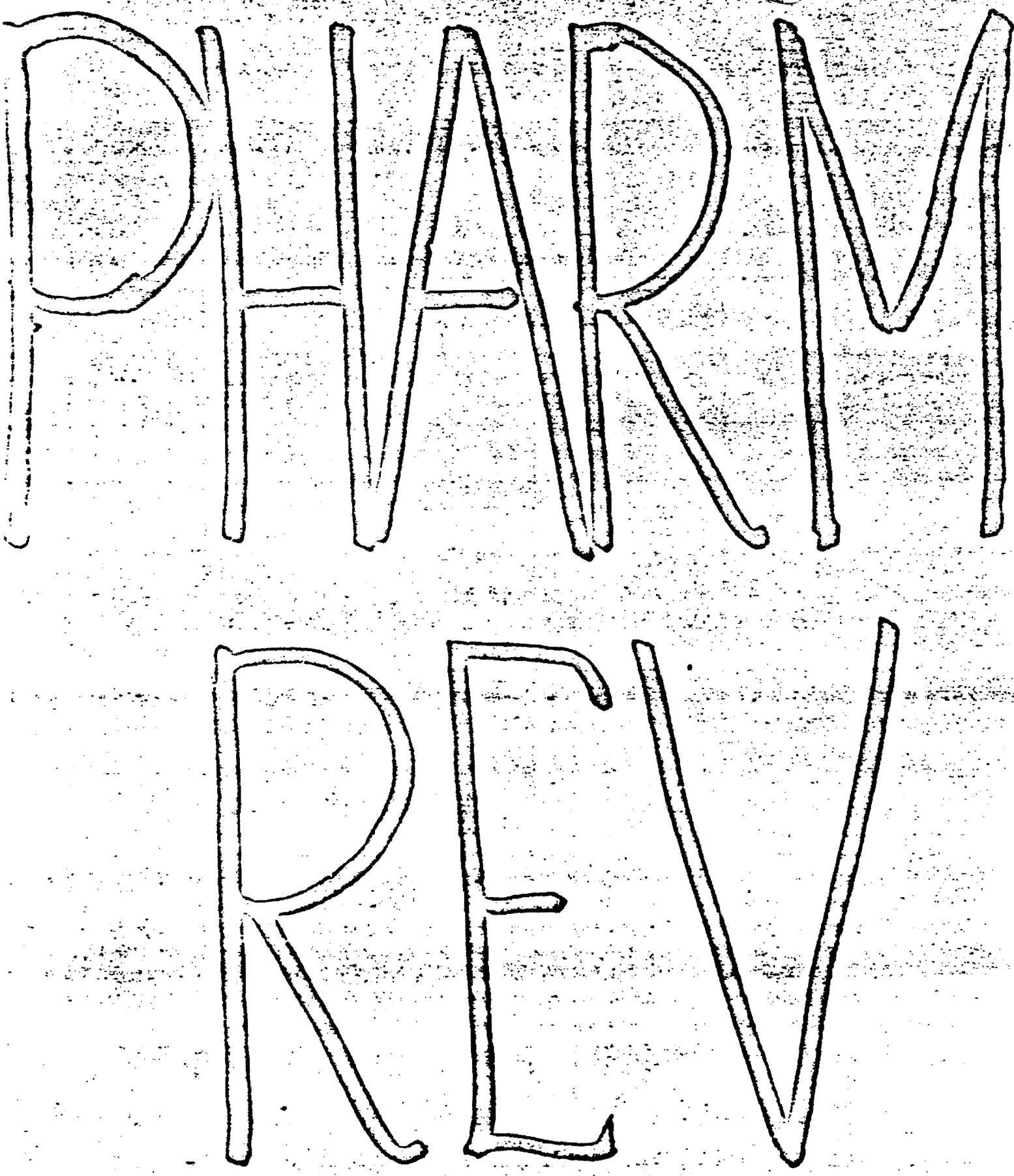

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Retrovir Capsules
(Zidovudine)

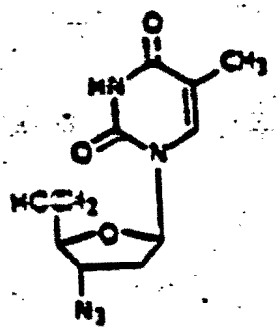
WARNING: THERAPY WITH RETROVIR (ZIDOVUDINE) IS OFTEN ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING GRANULOCYTOPENIA AND SEVERE ANEMIA REQUIRING TRANSFUSIONS (SEE WARNINGS).

IN ADDITION, PATIENTS TREATED WITH ZIDOVUDINE MAY DEVELOP OPPORTUNISTIC INFECTIONS (OI'S) AND OTHER COMPLICATIONS OF THE ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) AND AIDS RELATED COMPLEX (ARC) CAUSED BY THE HUMAN IMMUNODEFICIENCY VIRUS (HIV). THEREFORE, PATIENTS ON ZIDOVUDINE SHOULD BE UNDER CLOSE CLINICAL OBSERVATION BY INDIVIDUALS EXPERIENCED IN THE TREATMENT OF PATIENTS WITH DISEASES ASSOCIATED WITH HIV. THE SAFETY AND EFFICACY OF ZIDOVUDINE HAS NOT BEEN ESTABLISHED FOR PATIENTS OTHER THAN THOSE FOR WHOM IT HAS BEEN APPROVED (SEE INDICATIONS AND USAGE).

BOLD FACE TYPE

DESCRIPTION: RETROVIR is the brand name for zidovudine [formerly called azidothymidine (AZT)], an antiretroviral drug active against human immunodeficiency virus (HIV). RETROVIR Capsules are for oral administration. Each capsule contains 100 mg of zidovudine and the inactive ingredients corn starch, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The 100 mg empty hard gelatin capsule, printed with edible black ink, consists of gelatin, titanium dioxide, and other ingredients. The blue band around the capsule consists of gelatin, FD&C Blue No. 2 and other ingredients.

The chemical name of zidovudine is 3'-azido-3'-deoxythymidine; it has the following formula:



Zidovudine is a white to beige, odorless, crystalline solid with a molecular weight of 267.24 daltons and the molecular formula $C_{10}H_{13}N_5O_4$.

CLINICAL PHARMACOLOGY: Zidovudine is an inhibitor of the in vitro replication of some retroviruses including HIV (also known as HTLV III, LAV, or ARV). This drug is a thymidine analogue in which the 3'-hydroxy (-OH) group is replaced by an azido($-N_3$) group. Cellular thymidine kinase converts zidovudine into zidovudine monophosphate. The monophosphate is further converted into the diphosphate and triphosphate derivatives by cellular thymidylate kinase and possibly by other cellular enzymes. Zidovudine

triphosphate interferes with the HIV viral RNA dependent DNA polymerase, (reverse transcriptase) and thus, inhibits viral replication. Zidovudine triphosphate also inhibits cellular α-DNA polymerase, but to a lesser degree. In vitro, zidovudine triphosphate has been shown to be incorporated into growing chains of DNA by viral reverse transcriptase and to a much smaller extent by cellular α-DNA polymerase. When incorporation occurs, the DNA chain is terminated.

Microbiology: The relationship between the in vitro susceptibility of HIV to zidovudine and the clinical response to therapy has not been established, nor has the in vivo antiretroviral activity of zidovudine in humans infected with HIV been demonstrated (See CLINICAL TRIALS Section).

Zidovudine blocked 90% of detectable HIV replication in vitro at concentrations of $\leq$ 0.13 ug/ml (ID_{90}) when added shortly after laboratory infection of susceptible cells. This level of antiviral effect was observed in experiments measuring reverse transcriptase activity in H9 cells, PHA stimulated peripheral blood lymphocytes, and unstimulated peripheral blood lymphocytes. The amount of drug required to produce a 50% decrease in supernatant reverse transcriptase was 0.013 ug/ml (ID_{50}) in both H9 cells and peripheral blood lymphocytes. Partial inhibition of viral activity in cells with chronic HIV infection (presumed to carry integrated HIV DNA) required concentrations of zidovudine (8.8 ug/ml in one laboratory to 13.3 ug/ml in another) which are approximately 100 times as high as those necessary to block HIV replication in acutely infected cells. Because a limited number of virus isolates have been tested for sensitivity to zidovudine, these results may not accurately reflect the susceptibility of HIV strains causing disease in the general population.

In addition, sensitivity results vary greatly depending upon the elapsed time between virus infection and zidovudine treatment, the particular assay used, the cell type employed, and the laboratory performing the test.

The major metabolite of zidovudine, 3'-azido-3'-deoxy-5'-O-β-D-glucopyranuronsylthymidine (GAZT), does not inhibit HIV replication in vitro. GAZT does not antagonize the antiviral effect of zidovudine in vitro nor does GAZT compete with zidovudine triphosphate as an inhibitor of HIV reverse transcriptase.

Development of resistance to zidovudine has not been studied. The frequency of zidovudine resistant isolates existing in the general population and the rate of appearance of zidovudine resistant viral particles during treatment are unknown.

The cytotoxicity of zidovudine for various cell lines was determined using a cell growth assay. ID_{50} values for several human cell lines showed little growth inhibition by zidovudine except at concentrations 50 ug/ml. However, one human T-lymphocyte cell line was sensitive to the cytotoxic effect of zidovudine with an ID_{50} of 5 ug/ml. Moreover, in a colony-forming unit assay designed to assess the toxicity of zidovudine for human bone marrow, an ID_{50} value of 1.25 ug/ml was estimated. Two of six cell cultures tested were found to be sensitive to zidovudine at 5 ug/ml or less.

Zidovudine has antiviral activity against some mammalian retroviruses in addition to HIV. No significant inhibitory activity was exhibited against a variety of other human and animal viruses, except an ID_{50} of _____ ug/ml against the Epstein Barr virus, the clinical significance of which is not known at this time.

The following microbiological activities of zidovudine have been observed in vitro but the clinical significance is unknown. Many Enterobacteriaceae, including strains of Shigella, Salmonella, Klebsiella, Enterobacter, Citrobacter, and Escherichia coli are inhibited in vitro by low concentrations of zidovudine (0.005 to 0.5 ug/ml). Synergy of zidovudine with trimethoprim has been observed against some of these bacteria in vitro. Limited data suggest that bacterial resistance to zidovudine develops rapidly. Zidovudine has no activity against gram positive organisms, anaerobes, mycobacteria, or fungal pathogens including Candida albicans and Cryptococcus neoformans. Although Giardia lamblia is inhibited by 1.9 ug/ml of zidovudine, no activity was observed against other protozoal pathogens.

Pharmacokinetics: The pharmacokinetics of zidovudine has been evaluated in 22 adult HIV-infected patients in a Phase I dose-escalation study. Cohorts of 3 to 7 patients received 1 hour intravenous infusions of an investigational formulation of zidovudine ranging from 1-2.5 mg/kg every 8 hours to 2.5-7.5 mg/kg every 4 hours (3 to 45 mg/kg/day) for 14 to 28 days followed by oral dosing ranging from 2-5 mg/kg every 8 hours to 5-10 mg/kg every 4 hours (6 to 60 mg/kg/day) for an additional 32 days. After oral dosing, zidovudine was rapidly absorbed from the gastrointestinal tract with peak serum concentrations occurring within 0.5 to 1.5 hours. Dose-independent kinetics was observed over the range of 2 mg/kg every 8 hours to 10 mg/kg every 4 hours. The zidovudine half-life was between 0.78 to 1.93 hours.

Steady state serum concentrations of zidovudine following chronic oral administration of 250 mg every 4 hours (3.0 to 4.7 mg/kg) were determined in 20 patients (body weight ranged from 52.7 to 83.6 kg) in a Phase II trial. Mean steady state predose and 1.5 hours postdose zidovudine concentrations were 0.16 mcg/ml (range 0 to 0.84 mcg/ml) and 0.62 mcg/ml (range 0.05 to 1.46 mcg/ml), respectively.

Zidovudine is rapidly metabolized to 3'-azido-3'-deoxy-5'-O-β-D-glucopyranosylthymidine (GAZT) which has an apparent half-life of 1 hour (range 0.61 to 1.73 hours). Following oral administration, urinary recoveries of zidovudine and GAZT accounted for 14 and 74% of the dose, respectively, and the total urinary recovery averaged 90% (range 63 to 95%) indicating a high degree of absorption. As a result of first-pass metabolism, the average oral capsule bioavailability of zidovudine is 65% (range 52 to 75%).

Additional pharmacokinetic data following intravenous dosing indicated dose-independent kinetics over the range of 1 to 5 mg/kg with a mean zidovudine half-life of 1.1 hours (range 0.48 to 2.86 hours). Total body clearance averaged 1900 ml/min/70 kg and the apparent volume of distribution was 1.6 L/kg. Renal clearance is estimated to be 400 ml/min/70 kg, indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine plasma protein binding is 34 to 38%.

The zidovudine cerebrospinal fluid (CSF)/plasma concentration ratio measured 1.8 hours following oral dosing at 2 mg/kg was 0.15 (n = 1). The ratios measured at 2 to 4 hours following intravenous dosing of 2.5 mg/kg and 5.0 mg/kg were 0.20 (n = 1) and 0.64 (n = 3), respectively.

INDICATIONS AND USAGE: RETROVIR Capsules are indicated for the management of certain patients with symptomatic HIV infection (AIDS and advanced ARC) who have a history of histologically confirmed *Pneumocystis carinii* pneumonia (PCP) or an absolute T-helper cell (T_4) count of less than 200/mm^3 in the peripheral blood.

This indication is based primarily on the results of a randomized, double-blind, placebo-controlled trial conducted at 12 medical centers in the United States in which 281 adult patients with AIDS or advanced ARC were studied for an average of four and a half months. Additional data have been collected on approximately 80% of these patients who have received zidovudine in an open-label extension of this trial for an average of five more months (See CLINICAL TRIALS section).

In the placebo-controlled trial, all patients were begun at a dose of 250 mg orally every four hours. Hematologic toxicity resulted in dose reductions or discontinuations in 49 of the original 144 zidovudine recipients by the time the placebo-controlled trial ended (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections).

CONTRAINDICATIONS:

There are no known absolute contraindications to the use of RETROVIR capsules but extreme caution should be exercised in the administration of zidovudine to patients who are allergic or intolerant to the components of the formulation.

WARNINGS:

quite

Zidovudine has been carefully studied in fewer than 200 seriously ill HIV-infected patients for less than 6 months duration. Therefore, the full safety and efficacy profile of zidovudine has not been completely defined, particularly in regard to prolonged use, and especially in HIV-infected individuals who have less advanced disease (patients with T_4 counts greater than 200/mm^3).

Zidovudine should be used with extreme caution in patients who have bone marrow compromise evidenced by granulocyte count $< 1000/mm^3$ or hemoglobin < 9.5 gm/dl. In the placebo-controlled study, anemia and granulocytopenia were the most significant toxicities observed (See Adverse Reactions).

Significant anemia most commonly occurred after 4 to 6 weeks of therapy and in many cases required dose adjustment, discontinuation of zidovudine, and/or blood transfusions. Frequent (at least every 2 weeks) blood counts are strongly recommended in patients taking zidovudine. If anemia or neutropenia develops, dosage adjustments may be necessary (see Dosage and Administration).

Coadministration of zidovudine with other drugs metabolized by glucuronidation should be avoided because the toxicity of either drug may be potentiated (see Drug Interactions under PRECAUTIONS). Zidovudine recipients who used acetaminophen during the controlled trial had an increased incidence of neutropenia which appeared to be correlated with the duration of acetaminophen use.

PRECAUTIONS

General:

Zidovudine is eliminated from the body primarily by renal excretion following metabolism in the liver (glucuronidation). There are currently no data available concerning the use of zidovudine in patients with impaired renal or hepatic function, and such patients may be at a greater risk of toxicity from zidovudine.

Prolonged treatment with zidovudine may possibly result in selection of resistant viruses that may not respond to continued zidovudine therapy.

Information for Patients:

Zidovudine is not a cure for HIV infections, and patients may acquire illnesses including opportunistic infections associated with AIDS and ARC, particularly after 4 months of therapy. Therefore, patients should be advised to seek medical care for any significant change in their health status.

Patients should be informed that the major toxicities of zidovudine are granulocytopenia and/or anemia. They should be told that they may require transfusions or dose modifications including possible discontinuation if toxicity develops. They should be told of the extreme importance of having their blood counts followed closely while on therapy. They should be cautioned about the use of other medications that may exacerbate the toxicity of zidovudine.

RETROVIR Capsules are for oral ingestion only. Patients should be told of the importance of taking zidovudine exactly as prescribed, and that administration every 4 hours includes dosing around the clock, even though it may interrupt their normal sleep. They should be told not to share medication and not to exceed the recommended dose. They should be told that prolonged administration may be prescribed even though the long term effects are unknown at this time.

(not really?)

Patients should be advised that zidovudine therapy does not reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Drug Interactions
The interaction of other drugs with zidovudine has not been studied in a systemic manner. Coadministration of zidovudine with drugs that are nephrotoxic, are glucuronidated, interfere with RBC/WBC number or function, or affect DNA replication, may increase the risk of toxicity. Such drugs include, but are not limited to, trimethoprim-sulfamethoxazole (TMP-SMX), pyrimethamine, dapsone, pentamidine, amphotericin, flucytosine, vincristine, vinblastine, adriamycin, interferon, gancyclovir (DHPG), acyclovir, acetaminophen (See Warnings), indomethacin, and aspirin. Limited data suggest that probenecid may reduce renal excretion of zidovudine.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Long-term carcinogenicity studies of zidovudine in animals have not been done. However, in an in vitro mammalian cell transformation assay, zidovudine was positive at concentrations of 0.5 ug/ml and higher.

No evidence of mutagenicity (with or without metabolic activation) was observed in the Ames Salmonella mutagenicity assay. In a mutagenicity assay conducted in L5178Y/TK$^{+/-}$ mouse lymphoma cells, zidovudine was weakly mutagenic in the absence of metabolic activation only at the highest concentrations tested (4000 and 5000 ug/ml). In the presence of metabolic activation, the drug was weakly mutagenic at concentrations of 1000 ug/ml and higher. In an in vitro cytogenetic study performed in cultured human lymphocytes, zidovudine induced dose-related structural chromosomal abnormalities at concentrations of 3 ug/ml and higher. No such effects were noted at the two lowest concentrations tested, 0.3 and 1 ug/ml. In an in vivo cytogenetic study in rats, given a single intravenous injection of zidovudine at doses of 37.5 to 300 mg/kg, there were no treatment-related structural or numerical chromosomal alterations in spite of plasma levels that were as high as 453 ug/ml five minutes after dosing.

Effects of zidovudine on fertility have not been studied.

Pregnancy: Pregnancy Category C. An oral teratology study in pregnant rats using doses up to 20 times the human dose has revealed no evidence of harm to the fetus due to zidovudine. Teratogenicity testing and other reproduction/fertility tests in animals have not been completed. It is not known whether zidovudine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Zidovudine should be given to a pregnant women only if clearly needed.

Nursing Mothers: It is not known whether zidovudine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from zidovudine, mothers should be instructed to discontinue nursing if they are receiving zidovudine.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: The most frequent adverse events and abnormal laboratory values reported in the placebo-controlled clinical trial of oral zidovudine administration in 281 patients (144 patients zidovudine; 137 patients placebo) were granulocytopenia and anemia. The frequency of these adverse events is shown in the following table:

TABLE CENSORED

Because some patients were anemic and/or leukopenic before starting therapy with zidovudine, an alternative method of assessing decreased marrow function may be more appropriate, such as examining the degree of change when compared to baseline, shown in the table below:

TABLE CENSORED.

The anemia appeared to be the result of impaired DNA replication in erythrocyte precursors as evidenced by increasing macrocytosis (MCV) while on drug. In patients who developed significant anemia, dose reduction did not eliminate the need for transfusions. All patients who had dose reductions for anemia eventually required temporary discontinuation of zidovudine. _____ patients developed neutropenia ($< 500/mm^3$) without significant anemia. In many of these patients granulocyte counts increased despite continued zidovudine administration (usually at a reduced dose).

The following table summarizes those reported adverse events which occurred in at least 10% of patients in either the zidovudine or placebo groups.

TABLE CENSORED

Less frequent adverse events which occurred in $< 10\%$ of patients treated with zidovudine include: asthenia, malaise, diaphoresis, chest pain, chills, flu syndrome, generalized pain, cough, flatulence, dyspepsia, urinary frequency, dizziness, loss of mental acuity, bad taste in mouth, acne, arthralgia, back pain, bleeding gums, blurred vision, body odor, confusion, constipation, dysphagia, dysuria, edema of the lip, edema of the tongue, emotional lability, epistaxis, eructation, hearing loss, hoarseness, hyperalgesia, lymphadenopathy, mouth ulcer, muscle spasm, pharyngitis, photophobia, polyuria, pruritus, rectal hemorrhage, rhinitis, sinusitis, syncope, tremor, twitch, urinary hesitancy, vasodilation, and vertigo.

OVERDOSAGE: No cases of acute overdosage have been reported. If overdosage occurs, intensive observation for marrow suppression with transfusions and protective measures for granulocytopenia may be needed until marrow function returns. Although other nucleoside analogues have been partially removed by peritoneal or hemodialysis, it is not known whether zidovudine can be removed in this manner.

DOSAGE AND ADMINISTRATION:

The currently recommended starting dose of zidovudine in patients for whom the drug is indicated is 200 mg every 4 hours around the clock. Although all patients in the controlled efficacy trial were begun on 250 mg every 4 hours, this strength of capsule is not currently marketed (see CLINICAL TRIALS Section).

Careful monitoring of hematologic indices every two weeks is recommended in order to detect the development of serious anemia and neutropenia. In patients with hematologic toxicity, reduction in hemoglobin may occur as early as 2 to 4 weeks, and neutropenia usually occurs after 6 to 8 weeks.

Hematologic toxicities appear to be related to dose and duration of therapy.

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Dose Adjustment: Significant anemia (hemoglobin < 7.5 g/L or reduction of > 25% from baseline) and/or significant neutropenia (neutrophil count of < 750 mm^3 or reduction of > 50% from baseline) may require a dose interruption until some evidence of marrow recovery is observed (this may be for a period of up to 2 weeks). Alternatively, for significant anemia without neutropenia, red blood cell transfusions may be administered without a reduction in the dosage of zidovudine. In this case, hematologic indices should be monitored weekly and dosage reduced if transfusion requirements increase. For neutropenia without significant anemia, the dose of zidovudine may be reduced or discontinued until recovery of granulocyte count occurs. After 2 to 4 weeks at a reduced dose, gradual increases may be appropriate, depending on hematologic indices and patient tolerance.

HOW SUPPLIED:

CLINICAL TRIALS

The patient population of the controlled trial consisted of 160 AIDS patients (85 Retrovir and 75 placebo) who had recovered from their first episode of PCP diagnosed within the previous four months, and 121 ARC patients (59 Retrovir and 62 placebo) with multiple signs and symptoms of HIV infection, including mucocutaneous candidiasis and/or unexplained weight loss (>10% or>15 lbs) of prior body weight. All patients had evidence of impaired cellular immunity with an absence of delayed cutaneous hypersensitivity and a decreased number of T-helper (T_4) lymphocytes in the peripheral circulation. Two hundred twenty one (70%) of all patients had fewer than 200 T_4 cells/mm^3 at entry (9% of AIDS patients and 54% of ARC patients). The trial was stopped in September 1986 because of a significant reduction in mortality in the zidovudine group compared to the placebo group before all patients had completed the planned 24 weeks of treatment. Treatment duration ranged from 12 weeks to 26 weeks, with a mean and median duration of 17 and 18 weeks, respectively.

Administration of zidovudine resulted in a reduced mortality rate in this trial with 19 deaths in the control group and one in the RETROVIR group (all apparently due to opportunistic infections or other complications of HIV infection) at the time the trial ended ($p < .001$). All but one of the deaths occurred in patients with fewer than 200 T_4 cells at entry.

Administration of zidovudine reduced the risk of acquiring an AIDS-defining OI in patients with T_4 counts less than 200/mm^3 at entry. During the first six weeks of treatment, the number of OIs diagnosed in the zidovudine and placebo groups were similar (twelve in each group). After six weeks, 33 additional placebo recipients experienced at least one opportunistic infection compared to 12 additional patients treated with zidovudine. PCP was by far the most common OI diagnosed in both treatment groups.

The development of Kaposi's sarcoma during the controlled trial was not significantly different in the zidovudine group compared to the

Patients who received zidovudine generally did better than the placebo group in terms of several less definitive measures of efficacy. Most of the patients entered the study with high Karnofsky performance scores, a measure of functional ability. On average, zidovudine recipients retained this functional ability while in the placebo group it tended to decline. Zidovudine recipients tended to maintain their body weight, whereas placebo recipients tended to lose weight.

Patients receiving zidovudine experienced a modest but statistically significant increase in mean T-helper cell counts compared to the placebo group within 4 weeks of entry; the significance of this finding is unclear since T_4 counts declined again over the course of the study. Approximately a quarter of the zidovudine recipients developed at least a transient positive response to delayed hypersensitivity skin tests.

Although zidovudine is assumed to exert its beneficial effects by inhibiting HIV replication in vivo, an antiretroviral effect of the drug was not demonstrated in this trial despite frequent culturing of the peripheral blood lymphocytes for HIV. However, the methods used may have been relatively insensitive in detecting differences in the quantity of actively replicating virus.

At the conclusion of the placebo-controlled trial, patients in both treatment groups were offered the option of enrolling in an uncontrolled extension protocol in which all patients received open-label zidovudine at a dose of 200 mg every four hours. A slightly lower dose than that used in the placebo-controlled portion of the trial was chosen because of concern about cumulative hematologic toxicity at 250 mg q 4 h; production of a single strength 100 mg capsule was begun in order to conserve drug and achieve greater flexibility in dosing.

One hundred and twenty-seven (127) patients originally assigned to zidovudine and 100 patients originally assigned to placebo elected to participate in the open-label protocol after the placebo arm was discontinued. Over the following five months, 11 additional deaths have occurred and 40 more patients among the original Retrovir recipients have developed an AIDS-defining OI as of February 13, 1987, including twelve patients who have developed two or more OI's while on zidovudine. Thus, in the cohort of 144 patients originally randomized to zidovudine, a total of 12 deaths and 76 OIs in 64 patients had been reported as of February 13, 1987. The group was treated with zidovudine for an average of 38 weeks, with 85% of the original group completing at least 32 weeks of treatment. _____ patients (_____%) remain on therapy as of February 13, 1987. Of the _____ patients in the original zidovudine group who entered the placebo-controlled trial, ___% continue on therapy without dose modifications for toxicity. The risk of acquiring an OI increased after 18 weeks of therapy compared to the lower risk period between six and eighteen weeks. The risk of death also increased after 18 weeks. T4 counts have continued to decline with a mean value of _____at entry, _____at 16 weeks, and _____ at 32 weeks.